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A.M.A. ARCHIVES OF SURGERY

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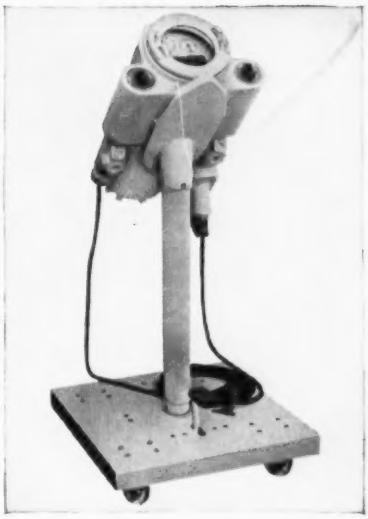

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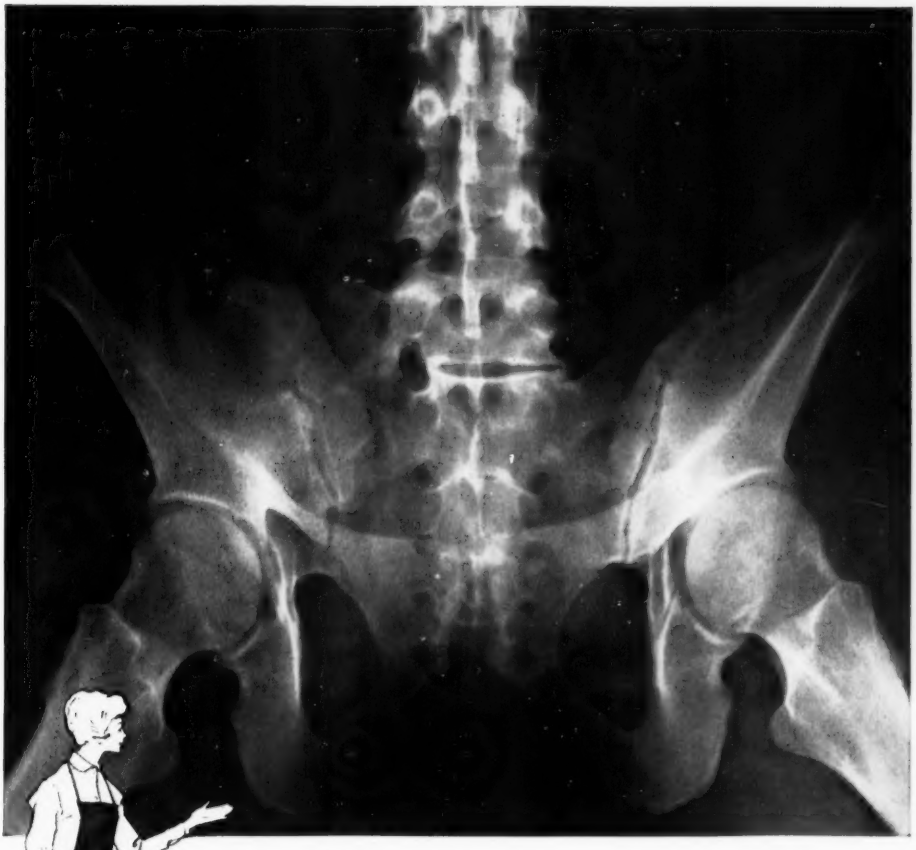

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JAMES BARRETT BROWN, M.D., St. Louis

We in medicine have a heritage coming down to us through the ages, from the widespread interest in writing about, and talking about, medicine and its problems. This can be taken as an inspiring challenge in our work. We know that there can never be perfection, and may feel about our patients as Marcus Aurelius did about his people, in that he could not give them what they deserved, or what he would like them to have. But he gave his life in trying, and left us part of our heritage from nonmedical sources.

For these reasons, it seemed worth while to look further into our situation, from the standpoint of what others may think of us, and write about us, in the pursuit of the ever-popular, and ever-present, subject of medicine and *the health of the individual.* Health problems, along with truth, as Socrates said, belong to everyone; and it is the public's right, and the right of literature, to present these problems for discussion—sometimes for condemnation, but more frequently for praise of our profession. Such public and literary discussions may serve us as sources in finding what we might mean to the public, and what we might be able to do, if we would concentrate on precepts that we were inspired with in our decision to follow this profession, and to which we hope to remain dedicated.

John Buchan, the author, who became Lord Tweedsmuir, Governor General of Canada, in his writing, contributes compliment and encouragement to the *individual,* and he has acute ability to suggest forthright endeavor in one's life. He has summed this up in one sentence: "You do not set up a mark to miss it." This is certainly an acceptable precept for surgery.

The trend of the general public and of literature is to hope, and suggest, that the man in medicine does as nearly perfectly as is possible. To repeat, I believe this can be taken as a heritage and as an inspiring challenge.

It is true that there are deviations from this theme and much antipathy to medicine and to doctors, but all of literature does not contain any more of these elements than appear in our own discussions, in our efforts to see that the best precepts are carried out by all concerned. We may learn, from each of these authors, items of help for us in our way of life. George Bernard Shaw, in "The Doctor's Dilemma," showed us the long-winded doctor, who was so boring in his speech and action that every one at a party was lulled to sleep by his incessant talk, and finally he himself succumbed to his own eloquence and dropped off, sound asleep, in the middle of one of his own speeches. Molière occupied himself, at length, in criticism of doctors.

From the Department of Surgery, Washington University Medical School.

President's address delivered at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 20, 1958.

Extreme interest in medicine runs throughout literature. For my part, having grown up a block from Mark Twain's home in Hannibal, it is natural to turn to Mark Twain. I was much saddened as a boy by the immense medical situation of poor young Dr. Robinson's having to open a grave, on the hill south of Hannibal, to extract the body of Hoss Williams so that he could better prepare himself for his task, and best serve his patients. He had hired Injun Joe and Muff Potter to go to the graveyard with him, and on this same night Huck Finn and Tom Sawyer happened to be there, for another medical reason, that of getting rid of warts. The boys, near the grave, looking for "spunk water," saw the eerie three approaching. After the body was out of the grave, Muff Potter, who was drunk as usual, held up Dr. Robinson for more pay and, as Muff had a knife in his hand, Dr. Robinson became frightened and hit him over the head with a grave board. During this scuffle, Muff dropped the knife, and Injun Joe grabbed it up and killed Dr. Robinson and then planted the knife on Muff Potter. Muff was exonerated only after a long, hard decision on the part of the boys, who feared Injun Joe's retaliation; however, Tom finally came through in the court scene, in which Injun Joe crashed through the window and escaped. Injun Joe was later located, dead, in the cave after it had been locked up, following the rescue of Tom and Becky Thatcher from it. This incident in this book meant a great deal to me as a boy, and it still does, because it expresses sympathy for the medical profession. It occurs as one of the most dramatic episodes in what Ernest Hemingway has called the classic American novel.

Tom's Aunt Polly was addicted to patent medicines, cramming them down Tom on every occasion, and one especially attractive pain killer that she dosed him with almost burnt him up. Soon thereafter the cat came fooling around Tom and the pain killer. Tom told the cat not to ask for any of the pain killer if he didn't really want it, but that if he really *did* want it he could have some. He carefully poured a dose into the begging cat's mouth, and the ensuing scene was one of destruction of the room. When Aunt Polly returned, she wanted to know what had happened to the house and the cat, and Tom said he had given the cat some pain killer, "because he had asked for it," and "because the cat didn't have any aunt to give it to him." Here, again, we see the ever-present idea of health and medication, and of manipulation of the human being for relief of discomfort.

Still another medical situation in "Tom Sawyer" is that of the schoolmaster who had been thwarted in his great desire to study medicine. The secret book that he read interminably in school, to the great amazement and inquisitiveness of the students, turned out to be a florid copy of anatomy, as Tom and Becky found out when she, unfortunately, tore one of the pages.

"Huckleberry Finn" uses smallpox as an excuse to keep two men, in a skiff, away from the raft where Huck has Negro Jim hidden, by suggesting that his deathly sick father is on the raft and needs help. They themselves assumed that Huck's father had smallpox; so, rather than risk exposure, they each put a $20 gold piece on a log, floated it down to Huck, and then went on without offering to help.

In contrast, the doctor, when Tom is shot in the leg, cares for the boy throughout the night on the same raft. We remember, too, that Jim will not run off, although this is his chance for freedom, but stays to help the doctor with Tom. It is pleasing to see the doctor's position in the book again, when he proves his moral courage in his defense of the Negro Jim from the crowd that had gathered to do him harm. The doctor is beautifully illustrated by Kemble as being the ideal type of person one *would* go to for help. It is apparent that the author picked out the medical profession to exhibit kindness, fairness, work, and willingness to help a stricken person. The self-sacrifice involved in risks taken daily by medical men has not been more touch-

ingly presented in American literature. It is sad that the schools of New York City have ruled out "Huckleberry Finn" from their libraries. No child shall be allowed to read it because the word "nigga" is in it, even though a Negro is the hero of the book. The perversions of literature still may be there, but "Huckleberry Finn" is ruled out. Many parents in New York probably will suggest that their children *do* read "Huckleberry Finn," so that this fair and honest and early evaluation of the situation may not be lost to them in their considerations.

"Life on the Mississippi" portrays the dramatic medical situation of Henry Clemens, Mark's brother, being burned to death in a steamboat explosion. The illustration showing Mark Twain in the hospital with his brother dying in front of him shows deep interest in the subject of burns. In the first edition of this book, on page 441, Mark Twain has his *own* image in the center of a group of flames. These flames are supposed to be the ultimate for Mark Twain, as they are hell-fire itself. A further interesting point is that in the second printing this illustration has been deleted, at the request of Mark Twain's wife, as she thought the illustration of the death of one member of the family from fire was enough.

Shakespeare is full of blood and thunder, but he also shows that the mental and bodily health of persons is of deep concern to him. The passage of Portia advising Shylock to "have by some surgeon, Shylock, on your charge, To stop his wounds, lest he do bleed to death," is perhaps the best known, and has the direct suggestion that a surgeon *would* be of benefit. It would have been good medicine to have had a Portia to help out with the psychiatric problems in "Hamlet."

The prevention of heart attack is described in "The Tempest," and has been beautifully illustrated in the Charles Lamb edition. Miranda thinks her dear lover, Ferdinand, is overtaxing his heart in carrying wood for the fire, and she offers to carry it, saying, "Alas, do not work so hard; pray rest yourself." Whereas there is comedy in this situation, there is still interest in medicine, besides which Miranda is giving good medical advice.

Since these medical elements have such intense interest, we might learn to use it to develop our public relations. In any event, we can accept these challenges that come to us as a heritage and can try to profit by them in our life's work.

Injuries of wars, of frontiers, of industry and traffic, and of the home, are with the populace throughout their lives. If we change mass into energy, if we have shooting wars, some one in going to get hurt, and some group needs to be there to help. For the frontier, we can go to the works of Alfred Henry Lewis, of early Arizona; these are illustrated by Frederick Remington, the first of which is on the cover of "Wolfville," wherein Texas Thompson is dispatching two or three undesirables with a gun in each hand. Depicted a little less dramatically, but forcefully, "a helpless short-horn stops both heels of a jackass in his mid-section." In these stories of "Wolfville," a leading citizen is Doc Petes; he is said to be the best-educated man in Arizona. He is looked up to for all sorts of good deeds, public effort, his surgery, his medicine, and for attending the birth of one baby in "Wolfville." A good example of a very brief operative report is that of the amputation of a horse thief's shattered leg, at the end of the story—"and humming a roundelay, Doc Petes cut merrily into the wounded member." In these tales of the old Southwest, medicine and surgery, in concept and in appreciation, are at the top of endeavor.

Items of medical interest occur back in antiquity, and from them may be learned important traits of character and of development, which still can be applied. For example, Democritus, about 400 B. C., was the first to use the word "atom" and used in its correct meaning of the time as something that could not be divided, or "without cutting." This laid the foundation for the concept of the elements, although its accept-

ance was delayed for about 2,000 years by Aristotle and his devoted followers, who stuck to his four elements only, of Earth, Air, Fire, and Water. Many must have questioned the work of Aristotle, but his influence could not be broken until the time of Galileo, Leeuwenhoek, Newton, and Gassendi, with their simple basis of theory and experiment. This situation has direct relation at present to all study and research, in that excessive pedantry, and inability to go forward or to avoid slotted information that can never be changed, may be taken as warnings to concepts in medicine. There need to be some persons who are allowed the most complete freedom to think, to foresee, and to experiment, in order to make advancements. A tremendous influence in one field may militate against acceptance of teamwork and of help from other fields that apply to the same problems. We in surgery, where the moment of actual work becomes so technical and personal, well realize that we must utilize the investigative work of others to give the most benefit to the individual patient.

As surgeons, we need to search for helpful adjuncts as much as anyone in medicine, because what happens to our patients is what we have done for them ourselves, not something delivered from a drugstore, or fought out along familial lines, or against some mental aberration. We are responsible as individuals for what we do for our patients, and we need the results of experimentation and the acceptance of help from other fields. Such help was often lacking during our own Civil War. At that time a surgeon, who was an authority on amputations, performed a large series in which the technique was perfect but, unfortunately, the patients all died of tetanus. Really good surgical results had to wait for bacteriology and immunology. I hope I may be excused for mentioning the results of cooperation of services in my own Army experience, in which there were no deaths in over 30,000 operations. The reason for this was that we used all the adjuncts and teamwork possible of anesthesia, medicine, radiology, laboratory, and other branches of medicine, working together to give the best to the patient. We know these facts from our own medical lore and literature, and we can find analogies in the general literature down through the ages.

In the Civil War literature by modern authors, again, we find acceptance of medical importance. A dramatic instance occurs in Shelby Foote's "Shiloh," where he describes the death of Gen. Albert Sidney Johnston. Dr. Yandell, his surgeon, argued against taking time to care for the fallen Northern soldier, but General Johnston cut him off with, "These men were our enemies a moment ago; they are our prisoners now. Take care of them." The sad thing about this is that General Johnston bled to death, just a little later, from a neglected wound from which he would have been saved if Dr. Yandell had not been caring for their prisoners. The needless loss of General Johnston was an extreme blow, and even more to Robert E. Lee was the loss of Stonewall Jackson, as recorded by Douglas Freeman. We remember that Jackson was shot, by mistake, by his own men. Dr. McGuire removed the arm, but the General died. This important medical situation has left us the beautiful final words of General Jackson: "Let us pass over the river and rest under the shade of the trees." When General Lee was told that General Jackson had lost his left arm, General Lee's comment was that, while Jackson had lost his left arm, he, Lee, had lost his right arm and he wished he could have been in General Jackson's place. These situations have nothing to do with sectionalism, but they point out, again, that we are the heritors of a tremendous feeling of hope for help from us on the part of the people of the world and of the authors that record their lives and their activities.

From ancient writings we may find instances of mistakes in interpretation and actual changes in concept of what the original authors intended. The popular idea concerning Epicurus' philosophy is a prime example of distortion of original intent.

His philosophy is usually interpreted as being intent on pleasure. The truth is that his pleasure was to be solely the lack of pain, to have peace of mind, or "ataraxis," as it was known so early in the world's history. He lived simply and frugally, did not stuff himself with food, and laid down rules of conduct with elements that could be followed today, to the world's advantage. His ideas of propagation of the race are not in accord with ours, but one seldom finds a book or a treatise in which every idea is acceptable. Epicurus was so much the devotee of *not* having pain that it would seem that somewhere in the field of anesthesiology the name of Epicurus should be included. He was generally, and finally, against pain and taught that being without pain produced the most pleasure in life. Epicurus was not the Epicurean of popular idea.

Epicurus, also, was one of the first to back Democritus on his atomic theory. He could not go along with the idea of the exact sameness of all atoms, however; and even back in that day of antiquity he maintained that there was some deviation of atoms in their constant activity. It is of great interest that now, in our own day, in 1957, a Nobel prize has been given for the finding that certain mesons of the atom *do* show deviation of movement. These things need not make each of us an agnostic, or a doubter, or lead us to feel that we cannot count on accumulated knowledge; but they do indicate that we can continue to experiment and prove, and show concern for facts which are not finally determined for us, and to keep open minds for improvement in our knowledge of the elements of our profession. One might even conjecture that, with the transmutation of the elements, Aristotle might be proved right with his Earth, Air, Fire, and Water, after all.

Lucretius, in "On the Nature of Things," is the one who gives us the data of Epicurus. Presumably, Epicurus *had* produced his own work but it did not survive, other than in this long poem of Lucretius. It is so long, and there are so many quasi statements and such lack of scientific observation, which, incidentally, was impossible in their time, that one tends to reject such works. Still it is apparent that we can gain a philosophical outlook concerning medicine from many places in the literature of the ages.

The "old philosopher" Lao-tze, born in 604 B. C., in "The Way of Life," suggests many things of value to medical concepts. He taught for a large number of years, but did not put anything down, since, in the words of Bynner, he had "decided that a great deal was done and said in the world which might better be spared." He believed in what has been called "creative quietism." He thought that a man could be a doer without being an actor. He was aware of the dangers inherent in dogma. He laid down no rigid laws for behavior other than that he thought men's conduct should depend on their instinct and conscience. He was saddened by men's tragic perversity and their indisposition to accept "The way of life." Lao-tze's philosophy of creative quietism, depending mainly on patience, forbearance, and fortitude, is so simple as to appear somewhat mystic, but nothing could have been farther from the thought of Lao-tze than to start a religion. The religion that followed this philosophy was a marked distortion of this simple precept; as Bynner says: "Men love to turn the simplest and most human of their species into complex and superhuman beings; thus everywhere men yearn to be mislead by magicians; thus cults in all lands under virtuous guise make of ethics a craft and a business."

As early as the sixth century B. C. Lao-tze said: "Can your learned head take leaven from the wisdom of your heart?" In this he suggests that the head *did* have the most to do with mind, and thought, as far as actions are concerned, and this was at a time when the seat of the mind was thought to be within the breast. Lao-tze did not know what cancer was, but a small part of his philosophy suggests the best that can be utilized, at present, for cancer.

He stated: "Men knowing the way of life face the simple fact before it becomes involved." "Solve the small problem before it becomes big." "The most involved fact in the world could have been faced when it was simple." "The biggest problem in the world could have been solved when it was small."

"A Doctor of the Old School," by Ian McClaren, contains dramatic praise of the medical profession. Alexander Woollcott has called this the finest descriptive and character writing in English. Among other things, it combines the value of cooperation between the general practitioner and the surgical specialist.

It concerns Dr. William Maclure, who practiced in Drumtochty, Scotland. A single horse could not do the work of this man, but he liked best his old white mare, called "Jess," who must have returned his liking, because she died a week after the doctor. He could ride faster and stay longer in the saddle than anyone in the parish, and it was all for mercy's sake. When Annie Mitchell was dying under his care, he called for help from Sir George, the Queen's surgeon, and had to drive him through the flooded Tochty River with great discomfort and danger. With the black waters racing all around the dogcart, Sir George's nerves were shaken, and he ordered Maclure to turn back, as he "would not allow himself to be drowned for any person." "Sit down," thundered Maclure, "Condemned ye will be sooner or later, if you shirk your duty, but through the water you are going today"; and Maclure prevailed. Annie Mitchell was saved by the surgical specialist out in this inaccessible mountain parish. Sir George would accept no pay, as he knew Dr. Maclure was going into his own pocket for the fee. As his returning train moved out, Sir George said: "Give us another shake of your hand, Maclure. I am proud to have met you; you are an honor to our profession. Look after Annie and mind the antiseptic dressings."

I shall ask the privilege of a personal insert here in relation to this very wonderful character in the old Scotland. My wife has a native Scot nephew who graduated at Edinburgh and who wanted to take care of families on the west coast of Scotland for the rest of his life, in some such manner as Dr. Maclure. Sadly and unfortunately, because of the National Medical Service, this young man was not allowed to inject this much personality and individuality into his work. He found that he could not stand the thought of this authoritarian life in his beloved country, and so he migrated to Western Canada for his life's work. I believe such instances are great losses to Scotland, and to the United Kingdom.

In such search as this for sources, one would naturally like to find some of the basic thought processes of the great names in scientific research. Although we may not know specifically of the work of those in other fields, we may try to understand *how* they think, and possibly find some application to our own problems. We, also, would find that it does take a real genius for great advancement, but we can learn from such persons how men of genius work. At the same time, it is found that a genius is a normal person except for the peculiar powers of reason which account for the great elements of progress.

Concerning research, Einstein has said: "Scientific research can reduce superstition by encouraging people to think and survey things in terms of cause and effect. Certain it is that a conviction, akin to religious feeling, of the rationality or intelligibility of the world lies behind all scientific work of a higher order." It is interesting to see the genius of Einstein in his deep appreciation of others' contributions. For example, concerning Newton, he said: "It is just two hundred years ago that Newton closed his eyes. It behooves us at such a moment to remember this brilliant genius who determined the course of Western thought, research and practice, to the extent that nobody before or since his time can touch."

Considerations of mental and physical health are often found in unexpected places.

I would like to repeat a short sentence of Longfellow's, which my mother had framed for me many years ago for my own room. Longfellow said, "If we could read the secret history of our enemies, we would find in each man's life sorrow and suffering enough to disarm all hostility." Here, again, is the theme of the human being suffering. It is uppermost in his mind through most of his life, and someone must be on hand to help.

As previously noted, all is not serious about the public's and literature's recognition of the medical profession. In "Tristram Shandy," written by Laurence Sterne, there are many medical situations, perhaps climaxed by Dr. Slop, in his curse that was nine pages long, directed at Obeideah, his servant. This was occasioned by Obeideah's having gone by horseback to get instruments for a delivery, but, having tied them so securely in the saddlebags, and having then galloped so furiously that the knot was pulled tight, Dr. Slop could not get it undone in time for the baby, and in the process cut his thumb "quite across to the very bone." None others have equaled this nine-page oath, although some may have been trying; but it is hoped that this will *not* be considered a challenge of literature.

Stephen Leacock, in "How to Be a Doctor," says:

> What I want to speak about is the progress of medicine. There, if you like, is something wonderful. Just think of it, a hundred years ago there were no bacilli, no ptomaine poisoning, no diphtheria, no appendicitis. Rabies was but little known and only imperfectly developed.
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> Or consider the advance of science on its practical side. A hundred years ago it used to be supposed that a fever could be cured by the letting of blood; now we know positively it can not. Even seventy years ago it was thought that a fever was curable by the administration of sedative drugs; now we know that it isn't. For the matter of that, as recently as thirty years ago, doctors thought that they could heal a fever by means of low diet and the application of ice; now they are absolutely certain that they can not. This instance shows a steady progress made in the treatment of fever.
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> In only one respect has there been a decided lack of progress in the domain of medicine. That is in the time it takes to become a qualified practitioner. In the good old days a man was turned out thoroughly equipped after putting in two winter sessions at a college, and spending his summers in running logs for a sawmill. Now it takes anywhere from five to eight years to become a doctor. Of course, one is willing to grant that our young men are growing more stupid and lazier every year. This fact will be corroborated at once by any man over forty years of age, but even when this is so, it seems odd that a man should require eight years now to learn what he used to acquire in eight months.

Leacock has a few more quips about diet, biopsies, and analytical laboratory work, and refers to Apollinaris and Scotch several times; but he goes on to say:

> And yet, isn't it funny you and I and the rest of of us, even if we know all of this about doctors, as soon as we have a pain within, rush for a doctor as fast as a hack can take us.

In this typical Leacock fashion, we find a summary of what we are talking about — that the people do have aches and pains and catastrophes and sadness, and they seek relief somewhere. These needs, these yearnings are the heritage of the medical profession. If we can convince the public that we feel that their troubles are a challenge and real concern to us, perhaps many of our difficulties may be made easier.

Medical advancement is somewhat like the dawn around the world, always occurring, every minute of the day, with slow but steady progress. There are occasional cataclysmic discoveries from training in observation, or by serendipity, and always there is our need and desire to "observe and record for mankind." Perhaps this literary heritage, this widespread interest in medicine, observed in the literature of the ages, can show us the true value of faith and spirit in our work, and thus be an inspiring challenge to our profession.

100 N. Euclid Ave.

Malignant Disease of the Head and Neck in Childhood

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The later decades of life are commonly those associated with malignant disease of the head and neck. The development in recent times of antibiotics and the widespread utilization of prophylaxis in the modification or prevention of the contagious diseases of childhood have resulted in a major change in the nature of the disorders producing pediatric morbidity and mortality. No longer do the infectious diseases and their complications occupy the preeminent role as the cause of death in infants and children. At the present time, exclusive of accidents, malignant neoplastic disease results in more deaths in the 4- to 15-year age group than any other single cause.

Just as tumor problems in general are more widely recognized as a critical source of pediatric disease, tumors in the regional area above the clavicles also are surpassing in importance certain of the more benign problems. A critical reevaluation of such disease in the head and neck may suggest certain definitive therapeutic procedures which offer some hope in the management of situations often considered to be totally unsalvageable.

There are two misconceptions associated with the treatment of malignant disease in childhood. The first of these stresses the insignificance of the problem. The preeminent position of malignant tumors as the cause of pediatric mortality belies this thesis. The second misconception is one which presupposes the futility of any management of such malignant disease. While the outlook is not ideal, application of certain principles of management has resulted in the salvage of a fair percentage of children so afflicted.

We have reviewed 70 cases of malignant disease of the head and neck area encountered during a 15-year period from 1942 through 1957. Intracranial disease and retinoblastomas have been excluded. This material was drawn both from the tumor service of the University of Illinois Research and Educational Hospitals and from our private practice. Divided in the broadest histologic sense, these patients presented 48 sarcomas and 22 carcinomas. Only one patient had a double primary malignant disease, a retinoblastoma and a chondrosarcoma.

Forty-three patients had as their presenting complaint a soft tissue mass in the neck without association with intraoral pathology.

TABLE 1.—*Sarcomas*

Lymphoma	23
Lymphosarcoma	12
Hodgkin's disease	11
Fibrosarcoma	8
Neurofibrosarcoma	4
Neuroblastoma	4
Rhabdomyosarcoma	4
Angiosarcoma	3
Miscellaneous	2
Total	48

Sarcomas

There were 48 patients whose tumor masses presented a pathologic picture consistent with sarcoma (Table 1). In this group there was almost an even distribution as to sex, with 27 male and 21 female patients (Table 2). The age distribution was somewhat different, as the incidence rose with age. In the 0- to 4-year age group there were 12 patients; in the 5- to 9-year age group, 15 patients, and in the 10- to 15-year age group, 21 patients (Table 3).

From the Department of Surgery, University of Illinois College of Medicine.

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TABLE 2.—*Sex Distribution*

	Carcinoma	Sarcoma	Total
Male	10	27	37
Female	12	21	33
Total	22	48	70

TABLE 3.—*Age Distribution*

Birth to 4 yr.	0	12	12
5 to 9 yr.	7	15	22
10 to 15 yr.	15	21	36
Total	22	48	70

Lymphoma.—The term lymphoma, as employed, implies lymphosarcoma, reticulum-cell sarcoma, or Hodgkin's disease. It should be noted that unless the lymphoma presented initially as a primary disease of the head and neck area without dissemination, it was not included in the series. Seven patients were classified as having lymphosarcomas. The over-all management of this group consisted primarily of biopsy, followed by irradiation, and occasional chemotherapy when systemic disease supervened. Four of these seven patients are alive and clinically free of disease 3, 6, 10, and 14 years following treatment, respectively. The longest survivor was a boy, who was first seen at the age of 15, with a swelling in the submandibular area of two years' duration. This was removed and found to be a large node consistent with lymphosarcoma. The patient received external x-radiation to the submandibular area at that time. He was well and clinically free of either local or systemic disease when seen a few months ago.

Twelve patients had Hodgkin's disease. This was frequently bilateral when first seen. Again, the treatment was primarily one of external x-radiation, supplemented when indicated by systemic chemotherapy. We (D. P. S. and H. W. S.) have reported elsewhere [1] a series of 18 patients with regionally localized Hodgkin's disease, who were treated surgically. One of the patients in the original series is a 15-year-old boy who is included in the present group. He first noticed a mass in the right midneck in January, 1952; and in March, 1952, the node was excised, followed by radical neck dissection. He has been well, without other evidence of disease since that time. Only two other patients have survived a significant period of time without evidence of either local or systemic disease. One was treated by irradiation, and the other, as part of a research study in 1946, solely with intravenous sterile mechlorethamine hydrochloride (nitrogen mustard). The latter patient was followed until 1951 and had regression of the primary disease and no further manifestation of systemic disease when lost to follow-up study. The average survival of the remaining patients was approximately 2 years, though one patient lived 10 years with disease. The youngest patient in this lymphoma group was 7 years of age.

TABLE 4.—*Status of Patients with Fibrosarcoma*

Location	Status *	Treatment †
Palate	NED 7½ yr.	S
Anterior neck	NED 7½ yr.	S
Posterior neck	NED 5 yr.	S
Buccal mucosa	NED 3½ yr.	S
Mandible	NED 3 yr.	S
Anterior neck	NED 3 yr.	R & S
Antrum	Dead 1½ yr.	S & R
Antrum	Dead 3 mo.	R

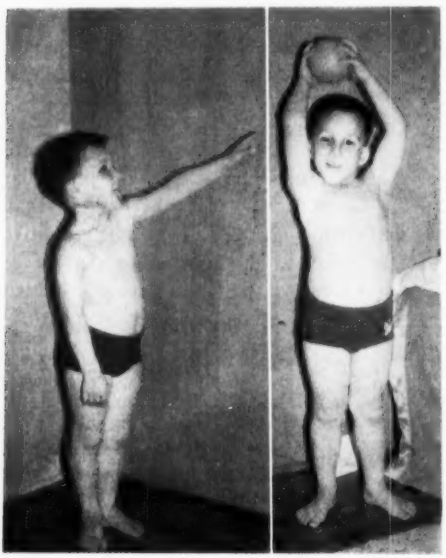
* NED-no evidence of disease.
† S indicates surgery; R, irradiation.

Fibrosarcoma.—A fibrosarcoma was encountered in eight patients. This particular tumor is classically radioresistent, and all these patients except one had their definitive management by the surgical approach (Table 4). The one patient (Case 8) treated by irradiation had a massive tumor involving the maxilla, cheek, and temporal area when first seen. She was treated with Co^{60} but died in less than three months after the diagnosis had been established. One child (Case 6) in particular points to the futility of irradiation in the over-all management of these tumors. The infant, a 14-month-old white boy, was seen in Oc-

tober, 1955, with the history that a mass had been noted in the right supraclavicular area in June, 1955. A biopsy performed at that time revealed a rather anaplastic, undifferentiated fibrosarcoma. This was treated by irradiation, with some initial regression but with prompt recurrence of the tumor mass. In October, 1955, a radical neck dissection was performed for removal of the tumor. The microscopic material at this time was consistent with the tumor originally removed. The child was reoperated on in March, 1956, because of four or five small nodules in the posterior cervical area. Microscopically, there was no evidence of residual disease; the specimen consisted of three small nodes with nonspecific lymphadenitis and two amputation neuromata of the cervical plexus. The child has been well, without evidence of disease since that time (Fig. 1).

Six of the eight patients in this group have survived free of disease for three to seven and one-half years following surgical extirpation of their tumor, three of them for over five years.

Fig. 1.—A boy, now aged 4 years, who had a fibrosarcoma of the right supraclavicular area at one year. Initial roentgen therapy produced only temporary remission. He has been without evidence of disease for three years following surgical removal. There is no significant functional deformity.



Neurofibrosarcoma.—The four patients with neurofibrosarcomas had a course similar to that of patients with the pure fibrosarcoma. Again, here, surgical extirpation of the disease was the treatment of choice. In a recent review[2] we noted that neurofibrosarcomas involving more deeply situated nerves lend themselves to a more effective en bloc excision of the tumor mass and proximal uninvolved nerve. The prognosis is distinctly better where this anatomic background exists. Three of the four patients presented themselves with deeply situated tumor masses and were treated by extensive resections. All three are alive 3½ to 14 years following surgery without evidence of additional disease. The one fatality in this group was initially seen as an 11-year-old boy with a neurofibrosarcoma of the upper lip. Repeated surgical extirpations were attempted, all of which of necessity were cosmetically deforming; each specimen demonstrated adequate margins of excision. Either because of multicentric origin along the proximal involved nerve or because of perineural lymphatic extension, repeated manifestations of recurrent disease presented until only orbital exenteration would allow possible extirpation of the tumor. Permission for this procedure was refused; the patient died approximately a year later, with intracranial extension. On the more favorable side, however, was the case of a 5-year-old girl who was admitted because of tracheal obstruction secondary to a tumor mass involving the anterior wall of the trachea.[3] A tracheostomy was performed, actually through the tumor mass, and a portion of the tissue removed at that time was consistent with the diagnosis of neurofibrosarcoma. It was possible at a secondary operative procedure to remove the tumor mass completely, as is shown in Figure 2, preserving both recurrent laryngeal nerves. Over the course of the next few years the patient had numerous plastic procedures reconstructing her trachea. The patient has made a complete adjustment,

Fig. 2.—A 5-year-old patient had a neurofibrosarcoma involving the trachea as shown. En bloc excision of the area was performed removing the strap muscles but preserving both recurrent laryngeal nerves and the membranous trachea which were uninvolved.

with a normal voice and satisfactory cosmetic appearance (Fig. 3), and was recently married. There has been no evidence of recurrent disease in 14 years.

Rhabdomyosarcoma.—Four patients had rhabdomyosarcoma; two of the tongue, one of the muscle of the cheek, and one presenting in the posterior cervical triangle. The first three patients were treated by irradiation and the last by surgery. One of irradiated patients survived two years with disease, while the other three were dead within six months.

Neuroblastoma.—The prognosis when a child develops a neuroblastoma primary in the head and neck area is almost universally poor. There were four patients in this group. Three of the four presented rather bulky lesions when first seen and the tumors were considered to be technically inoperable; the patients received x-ray therapy, with minimal palliation, and all were dead in less than nine months. The exception to this was a small child seen, first at the age of 6 months, with a large mass in the left side of the neck. This particular lesion was felt to be technically operable, and a left radical neck dissection was performed. This was followed with x-ray therapy to the left side of the neck. The patient has been well, without evidence of disease for the eight years following the operative procedure. It is also interesting to note that to date no apparent developmental abnormality has been associated with the roentgen therapy.

Fig. 3.—The same patient as Figure 2, 12 years following definitive surgery and reconstruction of the trachea. Her voice has a normal quality.

Angiosarcoma.—The angiosarcoma also is a rather aggressive childhood tumor. The lesion is not a particularly radiosensitive one, and at the same time its surgical removal is fought with discouragement. One patient in this group is alive, with intracranial metastases from her disease in less than a year following surgical treatment. Another is alive without evidence of disease one year following treatment, and the third died within three months after the diagnosis was established. This last case is of particular interest because, to our knowledge, it is the

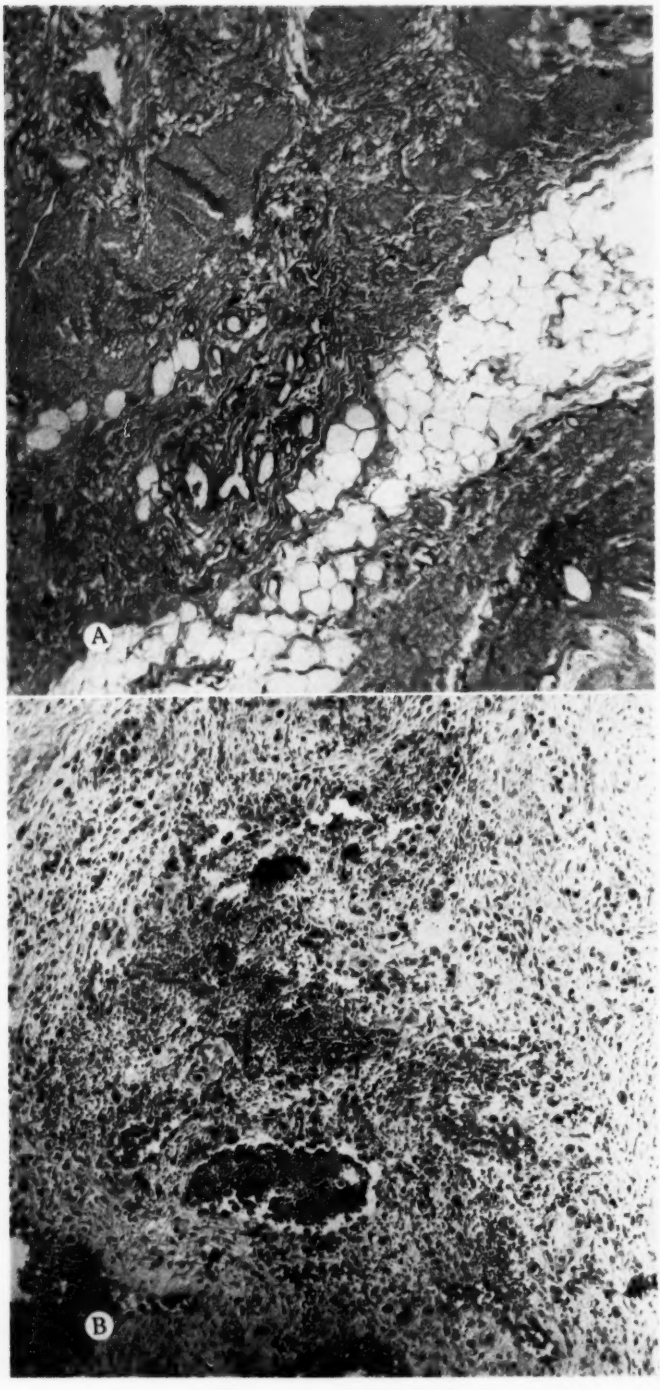


Fig. 4.—(*A*) This slide is a photomicrograph of a benign cavernous hemangioma in an 11-year-old girl which had previously been treated with sclerosing agents and radiation. (*B*) A specimen removed from the same patient one year later, revealing marked cellularity, pleomorphism, and mitotic figures consistent with a hemangiosarcoma. In spite of additional irradiaton, the child died within three months.

only one in which a benign cavernous hemangioma developed malignant degeneration (Fig. 4*A*). This girl was first seen at the age of 3 years with a mass in the right side of the neck, for which surgical excision was advised. She was treated elsewhere during the course of the next few years with intermittent external applications of x-radiation and the injection of sclerosing agents. She was seen again eight years later, with the mass still present in her neck, and an attempt was made at surgical excision. The lesion at this time was still benign. She was seen a year later, after a rapid increase in the size of the tumor mass, and surgical extirpation was again attempted. This was totally impossible at this stage and microscopically the lesion had become an angiosarcoma (Fig. 4*B*). The patient was treated by irradiation but died of hemorrhage within three months after the treatment was begun.

Miscellaneous Types.—Two additional sarcomas were encountered in this series: one a chondrosarcoma of the nose and the other a chordoma. The patient with the chordoma presented herself with a mass, for which surgical extirpation was attempted. This was followed by x-ray therapy, but the patient died with pulmonary metastases in seven months. The other patient died of what may well have been a radiation-induced sarcoma. The child had been treated elsewhere for a retinoblastoma at the age of 2 months, with enucleation of the orbital contents. There was local recurrence one year later, which was treated with radium-element application. Nine years later the child developed a tumor mass, which rapidly filled the orbital fossa and which, on biopsy, was found to be a chondrosarcoma. The child died within a month after the biopsy was performed and the diagnosis established. Autopsy revealed direct extension of the chondrosarcoma into the brain, but no evidence of residual retinoblastoma was detected.

Carcinomas

In contrast with the tumors encountered in the head and neck in the adult population, the carcinomas in children account for only about one-third of the malignant disease in this area (Table 5). Along this same line, the carcinomas develop in the older years of childhood (Table 3), and none of them appeared under the age of 5 years. There were 7 in the 5- to 9-year age group and 15 in the 10- to 15-year group. On the other hand, the sex distribution was approximately equal, with 10 male and 12 female patients developing tumors (Table 2).

TABLE 5.—*Carcinomas*

Thyroid	14
Salivary gland	4
Antrum	2
Gingiva	1
Skin	1
Total	22

Thyroid.—Fourteen patients have had the diagnosis of thyroid carcinoma established. Nine tumors were papillary adenocarcinoma and five were follicular adenocarcinoma. It is considered that thyroidectomy in conjunction with radical neck dissection and bilateral paratracheal-node dissection is the treatment of choice for papillary adenocarcinoma of the thyroid with or without clinical evidence of metastatic disease. This was the operation performed on all patients with this histologic type of tumor in the series. The majority of patients appeared with clinical evidence of disease at the time they were first examined (Fig. 5). Three patients had a modification of this form of management. In two of these cases the diagnosis of carcinoma was not established on frozen section but was apparent only when the permanent sections became available. One patient was treated prophylactically with external irradiation; the other was not. Each has had a long-term survival without additional evidence of disease. The other patient, who had only a thyroidectomy followed by irradiation, was a 12-year-old girl whose disease was locally sufficiently extensive that she had developed paralysis of one vocal cord, as well as direct invasion of

Fig. 5.—A 14-year-old girl with an adenocarcinoma primary in the maxillary antrum. A maxillary resection and orbital exenteration were performed, but disease was found to involve the cribriform plate. The patient died in nine months of intracranial extension.

the trachea and thyroid cartilage. Laryngectomy seemed to be an unreasonably mutilating procedure. The operative field was reopened 48 hours following thyroidectomy, and the area was implanted with interstitial radon. It should be noted that 10 of the 14 patients in this series who developed thyroid cancer in childhood had had previous external x-irradiation to the head and neck area.

All patients are surviving, though two are living with disease four and seven years respectively following the establishment of the diagnosis.

Salivary Gland.—Four patients developed lesions of the various salivary glands, three of parotid and one of minor salivary-gland origin. One of the tumors was a malignant mixed tumor in a 12-year-old girl; the other three were mucoepidermoid carcinomas, two in the parotid and one in a minor salivary gland of the buccal-gingival gutter. The patient with the malignant mixed tumor had had two previous local excisions with prompt recurrence. In 1945 a radical excision and neck dissection was performed for recurrent disease. She has been well since that time. One of the patients with a mucoepidermoid carcinoma of the parotid presented a fascinating diagnostic problem in that prior to the establishment of the diagnosis of the mucoepidermoid carcinoma the lad had had a microscopically proved diagnosis of tuberculous cervical lymphadenitis. An aspiration biopsy was taken from the cervical lymph nodes, in which the process had at one time subsided, but which had then begun to increase in size. This revealed metastatic mucoepidermoid carcinoma. A parotidectomy and radical neck dissection was performed, and the boy has been without evidence of disease for almost 10 years. Both of the other patients with salivary-gland carcinoma have similarly been without evidence of disease following definitive therapy.

Miscellaneous Types.—Two carcinomas of the antrum, one carcinoma of the gingiva, and one basal-cell carcinoma of the skin of the face were encountered. Both patients with carcinoma of the antrum, one an adenocarcinoma (Fig. 6) and the other a squamous-cell carcinoma, were treated first with maxillary resection, followed by radiation therapy. In one an orbital exenteration was included, with resection of the maxilla. Both patients died of recurrent disease within a year. In contrast, the patient with the squamous-cell carcinoma of the upper gingiva who underwent a partial resection of the maxilla has been well, without evidence of recurrent or metastatic disease for five years. This boy was 5 years old at the time of his original surgery. The final patient was a girl 8 years old at the time of her initial examination. At that time she had multiple basal-cell carcinomata of the skin of the face superimposed on xeroderma pigmentosum. Local excision of multiple lesions has been carried out throughout the

Fig. 6.—A 14-year-old girl who presented herself with an asymptomatic lateral neck mass, present for eight months. A firm nodule was palpable in the left lobe of her thyroid. Thyroidectomy and neck dissection were performed. She has been without evidence of disease for four years.

intervening nine years. She is alive, without evidence of progressive disease activity at the present time, though it has been only six months since her most recent surgical excision.

Comment

The most striking feature of the malignant disease process in children, in contrast with that in adults, is the preponderance of sarcomas over tumors of epithelial origin. Dargeon and associates [4] found this to be true for malignant disease in general in childhood, and this report confirms a similar finding of such disease in the head and neck area. Helmholz [5] found that 97% of malignant disease in childhood was of sarcomatous origin, in contrast with 90% for carcinoma in the adult.

Hayes Martin [6] has reported the largest previous series of malignant disease of the head and neck of childhood. In the report he reviewed his findings in 44 cases. Unlike the present study, Martin included retinoblastomas, of which there were 14 in his series, while omitting lymphomas. He emphasized that in children, just as in the adult population who present themselves with cervical lymphadenopathy, a search for a primary tumor before the scalpel descends upon the neck mass is of the utmost importance. While bilateral cervical lymphadenopathy in childhood is rather common, he felt that unilateral cervical-node enlargement or the presence of one node much larger than adjacent lymphoid structures should be cause for concern and investigation.

Presumptive diagnosis cannot be entertained with children any more than with adults. We have treated two "inoperable mandibular tumors" classified on a roentgenologic basis as osteogenic sarcomas. Biopsy and curettage were sufficient to eliminate the continued morbidity and anticipated mortality of the eosinophilic granulomata.

It is of the utmost importance that the misconception that malignant disease in childhood is almost universally fatal be dispelled. Certain histologic types of tumors, such as the rhabdomyosarcoma, do have essentially a universally fatal outlook. This, fortunately, is not true of all malignant disease, however. Fibrosarcomas and the neurofibrosarcomas, when recognized early

and adequately treated by proper definitive management, in general have a rather favorable outlook. In this particular series six of eight patients with fibrosarcoma and three of four with neurofibrosarcoma are living and well without evidence of disease from 1 to 14 years following treatment. Five of the twelve patients have survived free of disease over five years. Even with some of the less favorable lesions, however, such as the lymphomas and the neuroblastomas, occasional long-term survivals free of disease have been obtained when adequate definitive treatment has been undertaken early in the course of the disease. It might be said that with the majority of tumors the salvage rate could be expressed as a function not so much of the cell type as of the alertness of the physician to the possibility of the diagnosis of malignant disease and the prompt institution of adequate proper management without sentimental modification.

While carcinomas are not as common in the head and neck area as the sarcomas, cases of the former still present a statistically significant group. Thyroid carcinoma is the most frequent such tumor encountered in this series. While it is true that the mortality rate associated with thyroid carcinoma is not as high as with many other types of lesions, inadequate management leads to a coexistence with tumor which we prefer to avoid if it is possible to do so. Two of fourteen patients with carcinoma of the thyroid in this group are living with disease, while the remainder are free of disease from 1 to 17 years following treatment.

Squamous-cell carcinoma, so common in the adult, is unusual in childhood, but Moore [7] was able to collect over 40 authenticated cases from the world literature. One patient in this series with a squamous-cell carcinoma of the gingiva is living and well almost five years following a radical local excision of the hard palate, alveolar ridge, and a portion of the maxilla. Another patient with a squamous-cell carcinoma of the antrum died within a year of his disease.

The association of irradiation with the development of malignant disease in childhood in general, and specifically with thyroid carcinoma, has been the subject of widespread discussion in recent years. Winship and Chase,[8] as well as Clark,[9] initially called attention to this association between prior irradiation and carcinoma of the thyroid. About the same time, Simpson, Hempelmann, and Fuller [10] traced 1,400 children who had been treated with x-ray in infancy for thymic enlargement. At the same time as a control group, 1,795 siblings were evaluated. Both leukemia and thyroid carcinoma were found to be statistically higher in incidence than in the calculated expected rate or in the siblings. Meanwhile, approximately the same number of miscellaneous carcinomas developed in the treated group as in the control sibling population. In a later study,[11] involving 1,722 treated children and 1,933 siblings, the findings were similar with respect to thyroid carcinoma. Also noted more frequently in the treated group were benign tumors, as well as heart and mental disorders.

In the present study of cases of thyroid cancer (10 of which have been reported previously elsewhere [12]), 10 of the 14 patients had received previous irradiation. In no instance was the dosage given less than 200 r. Two other patients in this series are of interest in regard to the association of irradiation and childhood malignant disease. One of these was a child, aged 12 years, in whom there developed a hemangiosarcoma superimposed on a benign cavernous hemangioma, which had been present since birth. At different intervals during the age period of 3 to 7 years the child had had exposure to x-radiation, in an effort to retard the growth of the tumor mass. One year prior to the development of her malignant tumor, an attempt was made again to excise the lesion surgically, and the microscopic material at this time was entirely benign and consistent with diagnosis of a cavernous hemangioma. One year later, however, tissue removed was histologically a rapidly growing anaplastic angiosarcoma.

This is the only instance known to us in which a benign cavernous hemangioma has developed into a malignant, rapidly fatal disease process. The causal relation of the radiotherapy can be neither proved nor disproved. Another instance in which prior irradiation may have contributed to the development of malignant tumor is found in the child who died of a chondrosarcoma of the nasal bone. This patient had initially been treated, at the age of 2 months, by enucleation of the orbit for a retinoblastoma. A year later 9,600 mg-hr. of radium was delivered to an area of local recurrence. Ten years after this, at the age of 11, the child developed a chondrosarcoma, which rapidly filled the orbital space. She died of intracranial extension in less than a year.

Broadly speaking, the prognosis associated with malignant disease in childhood is not nearly as serious as is generally believed. A few years ago Pack and Ariel [13] reported a 42% five-year survival free of disease in 39 determinant cases of sarcoma of soft somatic tissues. In this series, while any individual group is too small for statistical evaluation, a reasonably good prognosis can be anticipated in those lesions in which the histologic type or anatomic location permits early adequate definitive management.

Dargeon [14] has emphasized that in the first five-year age group the potential salvage can be higher than that for any other segment of the childhood period. It is imperative, therefore, that the possibility of malignant disease be kept in mind by all who undertake the treatment of infants and children, and that any mass suspect of an anaplastic process be subjected to accurate diagnostic measures and, where indicated, prompt, definitive, and adequate management.

Summary

A series of 70 patients with malignant disease of the head and neck has been collected. Forty-eight tumors were sarcomas and 22 carcinomas.

While malignant disease in childhood is not a frequent cause of morbidity, it ranks second to accidents as the cause of mortality in the 4- to 15-year age group.

Awareness of the possibility of malignant disease and prompt institution of appropriate diagnostic and therapeutic measures are essential.

With this regimen, a favorable prognosis can be anticipated with such lesions, particularly, as fibrosarcoma, neurofibrosarcoma, and thyroid cancer.

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REFERENCES

1. Slaughter, D. P.; Economou, S. G., and Southwick, H. W.: Surgical Management of Hodgkin's Disease, Ann. Surg. 148:705, 1958.

2. Economou, S. G.; Southwick, H. W., and Slaughter, D. P.: Neurofibrosarcomas of Cranial Nerve Origin, A. M. A. Arch. Surg. 77:271, 1958.

3. Holinger, P. H.; Slaughter, D. P., and Novak, F. J., III: Unusual Tumors Obstructing the Lower Respiratory Tract of Infants and Children, Tr. Am. Acad. Ophth. 54:223, 1950.

4. Dargeon, H. W., and others: Round Table Discussion on Tumors, Benign and Malignant, American Academy of Pediatrics, J. Pediat. 30: 716, 1947.

5. Helmholz, H. F.: Malignant Neoplasms in Childhood, Proc. Staff Meet. Mayo Clin. 6:721, 1931.

6. Martin, H.: Cancer of the Head and Neck in Children, J. Pediat. 15:363, 1939.

7. Moore, C.: Personal communication to the authors.

8. Winship, T., and Chase, W. W.: Thyroid Carcinoma in Children, Surg. Gynec. & Obst. 101: 217, 1955.

9. Clark, D. E.: Association of Irradiation with Cancer of the Thyroid in Children and Adolescents, J. A. M. A. 159:1007, 1955.

10. Simpson, C. L.; Hempelmann, L. H., and Fuller, L. M.: Neoplasia in Children Treated with X-Rays in Infancy for Thymic Enlargement, Radiology 64:840, 1955.

11. Simpson, C. L., and Hempelmann, L. H.: Association of Tumors and Roentgen-Ray Treatment to the Thorax in Infancy, Cancer 10:42, 1957.

12. Majarakis, J. D.; Slaughter, D. P., and Cole, W. H.: Thyroid Cancer in Childhood and Adolescence, J. Clin. Endocrinol. 16:1487, 1956.

13. Pack, G. T., and Ariel, J. M.: Sarcomas of the Soft Somatic Tissues in Infants and Children, Surg. Gynec. & Obst. 98:675, 1954.

14. Dargeon, H. W.: Cancer in Children from Birth to 14 Years of Age, J. A. M. A. 136:459, 1948.

Asymptomatic Abdominal Masses in Infants and Children

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By careful abdominal examination of the infant or child, the physician may detect an abdominal mass which has not produced symptoms. The finding of an abdominal mass under these circumstances is of great importance to the patient, because it affords the physician the opportunity to treat the lesion not only when the possibility for cure is feasible but when the chance for cure can be greatly increased.

Accidents are still the greatest cause of death in children, and the second cause of death is benign and malignant tumors. During the past 15 years there has been a dramatic decrease in the death rate in infants and children from infectious diseases, so that today the juvenile population has increased. With this increase, the number of infants and children having an abdominal mass is potentially increased. The majority of abdominal masses in this age group are of congenital origin, and the time which elapses before symptoms are produced is variable. Any abdominal mass in an infant or child must be considered to be malignant until proved otherwise; therefore the responsibility of early diagnosis and an aggressive approach to these patients is to be encouraged.

In this paper, we have reviewed our personal experience during the past 16 years with patients in the pediatric age group who have been referred by their pediatricians on discovery of an abdominal mass on careful routine physical examination. There were no evident clinical symptoms directly referable to the mass in these patients.

Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 21, 1958.

From the Surgical Service of the Children's Hospital, Harper Hospital, and Wayne State University College of Medicine.

Wilms' Tumor—Renal Embryoma

Wilms' tumor, or renal embryoma, is the second commonest abdominal tumor in the infant and young child. Neuroblastoma is the commonest. Wilms' tumor has a tendency to grow anteriorly, making it easier to discover than neuroblastoma, which has a tendency to grow posteriorly in the retro-

TABLE 1.—*Wilms' Tumor—Renal Embryoma*

Case	Sex	Age	Side & Size of Tumor	Operation	X-Rays		Follow-Up	Comment
					Preop.	Postop.		
1	F	1 yr.	Left; filled entire abdomen	Nephrectomy	Yes	Yes	10½ yr.	Preop. x-ray shrunk tumor to 4 cm. diam.
2	F	5½ mo.	Right; 6 cm.	Nephrectomy	No	Yes	8 yr.	Well
3	M	8 wk.	Right; 12 cm.	Nephrectomy	No	Yes	7 yr.	Well
4	F	2 yr.	Left; 15 cm.	Nephrectomy	No	Yes	5½ yr.	5 mo. postop. bilat. pulm. met. disappeared c; x-ray therapy
5	F	3 yr.	Left; 24 cm.	Nephrectomy	No	Yes	14 mo.	Died
6	F	4½ yr.	Right; 22 cm.	Biopsy	No	Yes	5 mo.	Local invasion of diaphragm & liver; died
7	M	11 mo.	Right; 6 cm.	Nephrectomy	No	Yes	7 mo.	Well

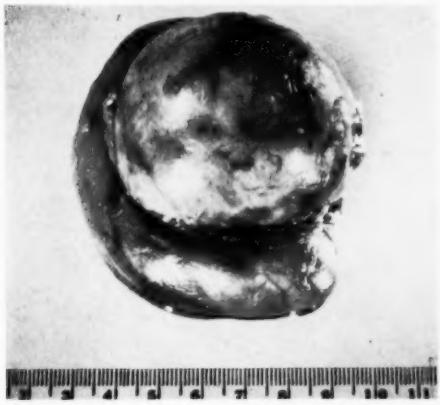


Fig. 1 (Case 2).—Photograph of operative specimen.

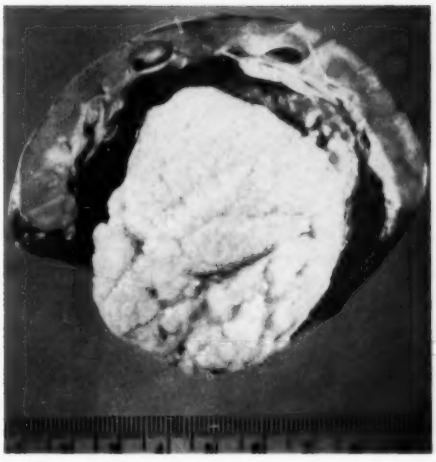


Fig. 2.—Photograph of transected specimen shown in Figure 1.

peritoneal area, so that its early detection by abdominal examination is more difficult.

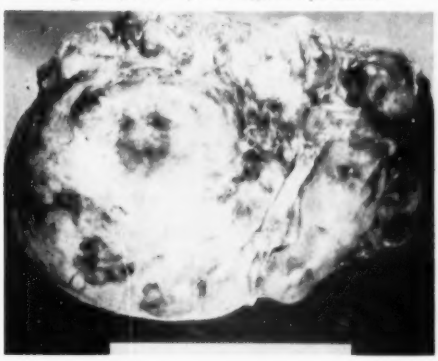
Of the seven patients in the group of Wilms' tumor (Table 1), six had a transabdominal nephrectomy and postoperative radiation therapy.

Preoperative x-ray therapy was given to only one patient (Patient 1), the tumor being so large in this one-year-old infant that we felt operative removal was too hazardous. Preoperative radiation reduced the size of the tumor in two weeks, and surgical excision was then accomplished with no difficulty. We agree with Gross [1] that preoperative x-ray therapy has been too widely used for Wilms' tumor, and we believe it should be used only in selective cases.

Fig. 3 (Case 4).—Intravenous pyelogram showing normal configuration on the left but no excretion on the right. The entire right half of the abdomen was occupied by a large embryoma.

When pulmonary metastases occur after transabdominal nephrectomy and postoperative irradiation, the postoperative time interval is usually four to eight months. Such metastasis did occur in Patient 4. This patient received a total of 2,340 r, divided in two series of radiation therapy, in the first three months following operation. Bilateral pulmonary metastases were found

Fig. 4 (Case 4).—Surgical specimen.



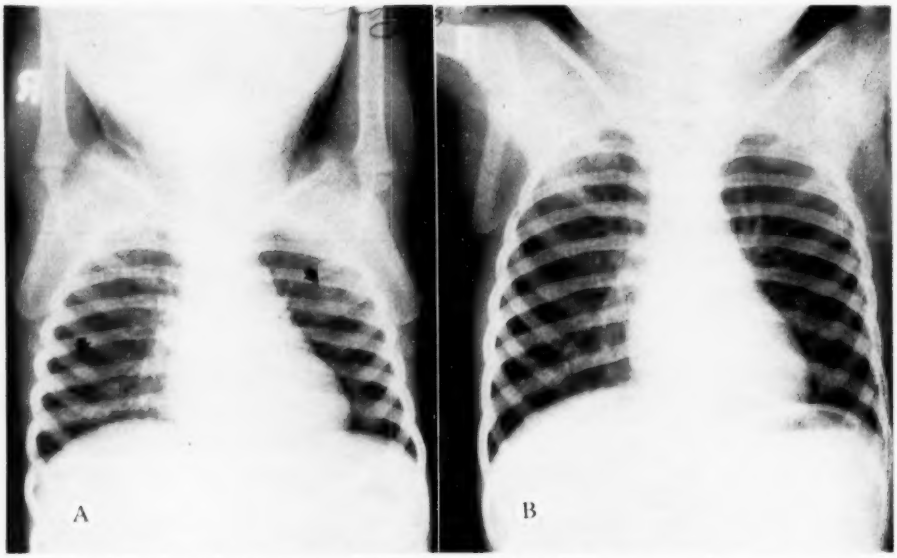


Fig. 5 (Case 4).—*A*, arrows pointing to metastatic lesion in each lung five months after operation; *B*, lung fields clear five and a half years later.

on the check-up chest film five months after operation. The prognosis appeared hopeless in view of the bilateral pulmonary metastases. Irradiation of both lung fields was instituted, the first series, over a one-week period, consisted of 780 r over the anterior chest and 780 r over the posterior chest. Two months later an additional 390 r was administered anteriorly and posteriorly, over a four-day period. The pulmonary metastatic areas responded extremely well to radiation therapy, all evidence of metastases having disappeared three months after the first series of radiation therapy over the lung fields was instituted. It is now five and one-half years since and this patient is in excellent health.

Unilateral Multicystic Kidney and Congenital Hydronephrosis

Genitourinary masses make up about 50% of abdominal masses in infants and children. In Table 2 there are listed four patients who were operated upon for unilateral multicystic kidney disease. All these infants were under one year of age; after nephrectomy, three made excellent recoveries, and one died five months postoperatively of associated congenital heart disease. Unilateral multicystic kidney disease occurs

TABLE 2.—*Unilateral Multicystic Kidney and Congenital Hydronephrosis*

Case	Sex	Age	Diagnosis	Operation	Follow-Up	Comment
8	F	5 mo.	Lt. multicystic kidney	Nephrectomy	1 yr.	Well; lost to follow-up
9	M	5½ mo.	Rt. multilocular cyst of kidney	Nephrectomy	9 yr.	Seen by family physician for URI
10	M	3 mo.	Rt. hydronephrosis, hydroureter	Nephrectomy; ureterectomy	5 yr.	Well
11	M	4 wk.	Lt. multicystic kidney	Nephrectomy	5 mo.	Died; congenital heart disease
12	M	10 wk.	Lt. multicystic kidney	Nephrectomy	10 mo.	Well
13	M	17 mo.	Double kidney c hydronephrosis & hydroureters	Nephrectomy & ureterectomy, rt. side	3 yr.	Well

Kidneys of the opposite sides were all normal.

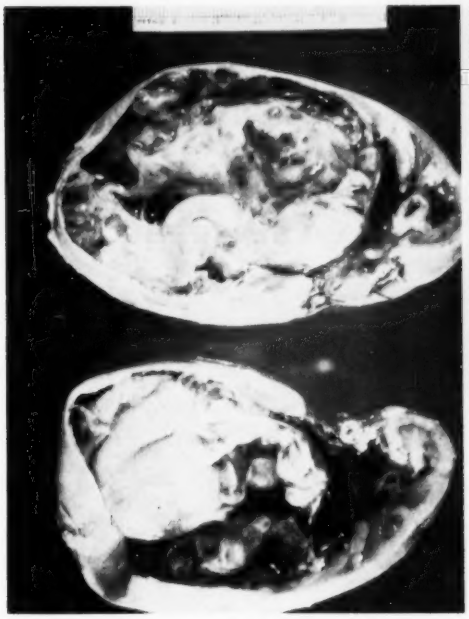


Fig. 6.—Unilateral multicystic renal disease.

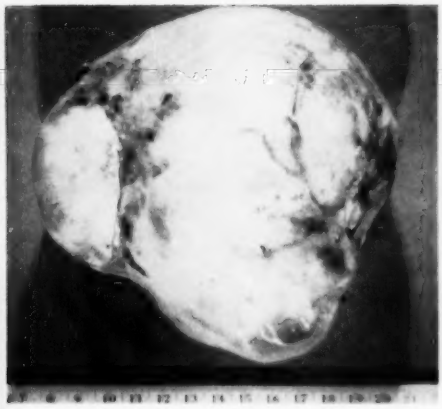


Fig. 7 (Case 15).—Retroperitoneal teratoma.

in about 0.1% of infants. The renal parenchyma is hypoplastic and destroyed. Spence [6] has emphasized that this condition is a distinct entity and should be distinguished from polycystic disease of the kidney. The latter lesion implies heredity, bilaterality, progression, and death. Spence collected 15 cases of congenital unilateral multicystic disease of the kidney from the literature and added four of his own, in which treatment was successful. Two of the four patients were in the pediatric age group. Longino and Martin [7] found 13 cases in the neonatal period, and in all instances the opposite kidney was normal in the initial intravenous pyelogram and has remained so.

In Table 2 are listed two patients who presented renal masses due to congenital ureteral obstruction with secondary hydroureter and hydronephrosis. Nephrectomy and ureterectomy in each instance resulted in excellent recoveries.

Teratoma

Abdominal teratoma is most commonly associated with the ovary, but occasionally a retroperitoneal teratoma is encountered in infants and children. Arnheim [11] has emphasized that these tumors in the retroperitoneal area should all be removed, for all reported untreated patients have died. These tumors may contain malignant tissues. In Case 15 (Table 3) the tumor was approached by opening the lesser sac, and the mass was seen to the left side of the midline close to the pancreas and left kidney.

Teratoma of the ovary is not very common in the pediatric age group, but we have operated in 14 cases over a 22-year period. Nine of these patients were emergencies because of torsion of the pedicle with subsequent infarction. All of these patients recovered after surgery. In Case 14 there

TABLE 3.—*Teratoma*

Case	Sex	Age	Diagnosis	Operation	Follow-Up	Comment
14	F	4 yr.	Teratoma; rt. ovary	Excision rt. ovary	7½ yr.	Well
15	M	10 mo.	Retroperitoneal teratoma	Excision of tumor	6 yr.	Located in lesser sac encapsulated
16	F	5½ yr.	Teratoma, lt. ovary	Exc. lt. ovary and Fallopian tube	3 yr.	Well

Fig. 8 (Case 16).—Ovarian teratoma before surgical removal.

were no symptoms referable to the tumor, and it was found on routine physical examination by the pediatrician. The operative finding is shown in Figure 8.

Hamartoma

Hamartoma is a developmental lesion of the liver and is extremely rare. It is not a neoplastic growth, but the mass contains imperfectly formed liver lobules, biliary ducts, and possibly vessel networks in a purposeless arrangement. Surgical removal is indicated because this lesion can grow rapidly and cause pressure on neighboring organs, especially the duodenum. Ladd and Gross,[9] Benson and Penberthy,[3] Patton,[8] and Speirs,[10] have each reported successful cases in infants. In Case 17 (Table 4) the excised tumor mass weighed 60 gm., and the mass in Case 18 measured 9 cm. in diameter. Prognosis after surgical excision is excellent, as complete removal is possible because this lesion is well demarcated and benign.

TABLE 4.—*Hamartoma*

Case	Sex	Age	Diagnosis	Operation	Follow-Up	Comment
17	F	7 mo.	Hamartoma of rt. lobe liver	Excision of tumor	16 yr.	Well
18	F	1 mo.	Hamartoma of rt. lobe liver	Excision of tumor	2 yr. 9 mo.	Well

TABLE 5.—*Miscellaneous Abdominal Masses*

Case	Sex	Age	Diagnosis	Operation	Postop. x-ray	Follow-Up	Comment
19	M	3½ yr.	Papillary adenocarcinoma left kidney	Nephrectomy	Yes	4½ yr.	Well; mass found during physical exam. for T. A.
20	M	2 yr.	Duplication of ileum	Resection of part of ileum & duplication	No	1 mo.	Well
21	F	2½ yr.	Rhabdomyosarcoma of bladder, bowel & abd. wall	Resection of tumor & part of ileum	Yes	6 mo.	Died; extension of disease
22	M	4 days	Saccular aneurysm abd. aorta & aneurysm of rt. iliac artery	Explor. lap.	No	4 mo.	Died; rupture of aneurysm of rt. common iliac a.
23	M	2 mo.	Chylous cysts of mesentery	Resection of cysts & part of ileum	No	4 yr.	Well
24	M	9 days	Lt. retroperitoneal neuroblastoma	Exc. of mass	Yes	Lost to follow-up. Completed only first course roentogen therapy	
25	M	5 yr.	Rt. retroperitoneal neuroblastoma	Exc. of mass	Yes	14 mo.	Died generalized metastasis
26	F	20 mo.	Lt. retroperitoneal neuroblastoma	Explor. lap; biopsy	Yes	5 yr.	Well

Miscellaneous Abdominal Masses

This group, of eight patients, presented varied lesions, as tabulated in Table 5.

Of the eight patients, five presented highly malignant tumors, and only two are surviving and well four and a half to five years after treatment. Patient 22, who was 4 days old at time of laparotomy, presented a very unusual finding in that of a pulsating, bilobed mass at the level of the aortic bifurcation. No definitive surgical procedure was possible, and the patient died at 4 months of age of rupture of the right iliac aneurysm. In Figure 9 the rupture of the right iliac aneurysm is seen, and there was an associated saccular aneurysm of the abdominal aorta below the level of the renal vessels. This is a most unusual lesion and is the first one we have encountered.

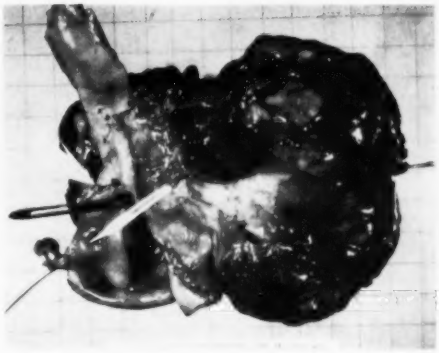


Fig. 9 (Case 22).—Postmortem specimen showing rupture of right iliac aneurysm and huge saccular aneurysm of abdominal aorta.

Case 20 presented also an unusual lesion at laparotomy, namely, a duplication of the ileum. Duplication of the ileum in infants is not common, and in the case reported the duplication was 6 in. (15 cm.) long and had its origin on the mesenteric side of the bowel with a common blood supply. The lumen of the duplication had no communication with the normal ileal lumen. From a clinical standpoint, the duplication was discovered as a movable mass, which could be shifted from one quadrant to the other in the lower abdomen. Resection of the duplication and corresponding segment of ileum and end-to-end anastomosis was followed by complete recovery.

Another unusual tumor (Case 19) for this age group was that of papillary adenocarcinoma of the left kidney. This patient, a white boy 3½ years old, had a large flank mass. Nephrectomy by the transperitoneal route allowed us to isolate the renal pedicle vessels before manipulating the tumor. His postoperative course was uneventful, and during the immediate postoperative period radiation therapy, consisting of 1,560 r, was administered to the left abdominal area anteriorly and posteriorly in a two-week period. A second series, two months later, consisted of administration of 1,950 r over the same field over a

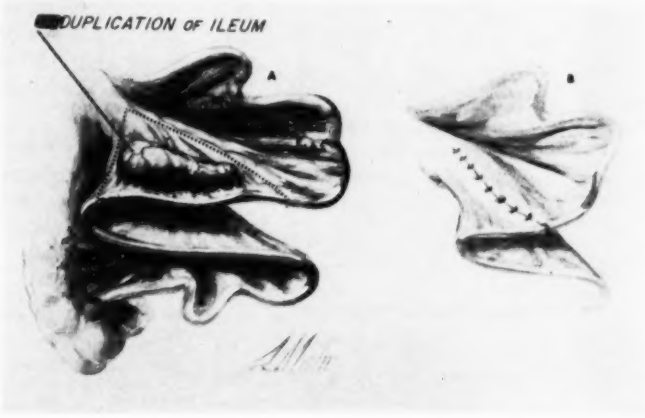


Fig. 10 (Case 20.)—Drawing of duplication of ileum and operative procedure accomplished.

TABLE 6.—*Results of Operation in Fourteen Benign Masses*

Doing well		11
Died		2
Ruptured aneurysm of rt. common iliac artery	1	
Congenital heart disease	1	
Lost to follow-up		1
Survival		78.5%

TABLE 7.—*Results in Twelve Malignant Masses*

		Comment
Papillary adenocarcinoma	1	Doing well 4½ yr. postop.
Neuroblastoma	3	1 Lost to follow-up 1 Died 14 mo. postop. widespread bone metastasis 1 Doing well 5 yr. postop.
Rhabdomyosarcoma	1	Died of recurrence 6 mo. postop., bladder & rt. colon
Wilms' tumor	7	5 Doing well, average 5½ yr. postop. 2 Died — Ave. 8½ mo. post-op. — 1 Biopsy, nephrectomy, & radiation; 1 Nephrectomy

Survivals 50% — 6 patients, average 5 yr. postop.

10-day period, and a final series, consisting of 1,560 r given over the same field, was completed two months after the second series. A total of 5,070 r was administered in the completed series. This child is entirely well, four and a half years after nephrectomy. Johnson and Marshall,[12] in a review of renal tumors in children encountered over a 25-year period at their institutions, found 59 Wilms' tumors, 3 papillary adenocarcinomas, and 2 renal-cell carcinomas. Papillary carcinoma, when it does occur, usually does so in older children and adults.

A summary of results is presented in Tables 6 and 7. A 78.5% survival rate and cure in the 14 infants and children with benign abdominal masses emphasizes the opportunity for salvage the patient and surgeon can expect from surgical excision of the mass. In the 12 infants and children who had a malignant abdominal mass, a survival rate of 6 patients, with an average of five years' follow-up after operation, and the fact that in each instance the patient is in good health and has no evidence of recurrence, offer encouragement to the surgeon to try to salvage as many of these patients as possible. It is evident from a review of the patients with Wilms' tumor who are under one year of age that the prognosis is very favorable. In this series of seven patients, four were under one year of age at the time of surgery, and the latter are all living and with no evidence of recurrence after 7, 8, and 10½ years, in three cases, and after 7 months, in the most recent case.

Summary and Conclusions

Every infant or child who presents an abdominal mass should have a scout film of the abdomen, an intravenous pyelogram, a complete blood count, and urinalysis preoperatively.

Every mass in an infant or child should be considered to be malignant until proved otherwise.

In this series of 26 infants and children in whom an asymptomatic abdominal mass was found on physical examination, 12 were proved to be malignant, with an overall survival rate of 58%.

Of eight patients with a malignant renal lesion, five are surviving and free of disease from 4½ to 10½ years following transabdominal nephrectomy and radiation therapy. An additional infant, operated upon for Wilms' tumor, is well seven months postoperatively.

One of three patients with neuroblastoma is surviving and free of disease five years after biopsy and radiation therapy.

Of the 14 infants and children presenting a benign abdominal mass, 11, or 78.5%, are living and well. One recovered completely but was lost to follow-up one year after operation.

From this study of 26 infants and children with an asymptomatic abdominal mass, 2 were lost to follow-up. Of the remaining 24 patients followed, 18, or 75%, are surviving and well. These results emphasize that if an asymptomatic mass can be detected in an infant or child before obvious clinical symptoms occur, the prospect for survival and cure is encouraging.

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REFERENCES

1. Gross, R. E.: The Surgery of Infancy and Childhood: Its Principles and Techniques, Philadelphia, W. B. Saunders Company, 1953.

2. Thompson, I. M.; Schneider, J. P, and Nickell, L.: Genitourinary Neoplasms in Infancy and Childhood, Texas J. Med. 53:919-924, 1957.

3. Benson, C. D., and Penberthy, G. C.: Surgical Excision of Primary Tumor of Liver (Hamartoma) in Infant 7 Months Old with Recovery, Surgery 12:881-886, 1942.

4. Swenson, O.: Pediatric Surgery, New York, Appleton-Century-Crofts, Inc., 1958.

5. Wineberg, S. R.; O'Connor, W. J., and Senger, F. L.: Unilateral Multicystic Renal Disease of the Newborn, A. M. A. J. Dis. Child. 92: 576-580, 1956.

6. Spence, H. M.: Congenital Unilateral Multicystic Kidney: An Entity to Be Distinguished from Polycystic Kidney Disease and Other Cystic Disorders, J. Urol. 74:693-706, 1955.

7. Longino, L. A., and Martin, L. R.: Abdominal Masses in the Newborn Infant, Pediatrics 21: 596-604, 1958.

8. Patton, R. J.: Hamartoma of Liver, Ann. Surg. 127:180-186, 1948.

9. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941.

10. Speirs, R. E.: Personal communication to the authors, 1958.

11. Arnheim, E. E.: Retroperitoneal Teratomas in Infancy and Childhood, Pediatrics 8:309-327, 1951.

12. Johnson, H. S., III, and Marshall, M., Jr.: Primary Kidney Tumors of Childhood, J. Urol. 74: 707-720, 1955.

DISCUSSION

DR. WILLIAM H. SNYDER JR., Los Angeles: I appreciate being asked to comment on this fascinating and worth-while paper. Dr. Benson gave us a little preview of it.

Eight years ago we presented before this Section a clinical study of 88 patients with retroperitoneal tumors from the Los Angeles Children's Hospital. Although one-half, or 44 patients, were brought to the hospital because of an enlarging abdomen or because a mass had been palpated, we did not analyze separately the well children in whom a mass had been found on routine examination. This idea which Dr. Benson has illustrated is of clinical significance. It emphasizes especially the importance of routine abdominal examination in infancy and childhood. When such a group is analyzed, as Dr. Benson has done, one becomes optimistic and enthusiastic. This will lead to improved results. He found a high percentage of benign tumors, whereas in our series they represented only 3%. The salvage rate was much, much higher when the cases without symptoms were considered separately. The over-all salvage in our group was only 20%. The entity "benign unilateral cystic disease of the kidney" has been well illustrated in this report. It is somewhat surprising that we did not find one case in our 14-year study. We agree with Dr. Benson's energetic surgical approach. However, we also use preoperative x-ray therapy on those patients with really massive Wilms' tumors. We feel that the child's condition can be improved during this therapy and the technical difficulties minimized thereby. We have been impressed by the frequency of positive bone-marrow biopsies on patients with neuroblastoma. However, we are encouraged even under these circumstances by the postoperative x-ray therapy and by the results when this therapy is combined with tetracycline (Achromycin B). Although we feel that the tumor eventually recurs, the action of tetracycline in metastasis has been spectacular in some patients.

DR. JACOB BERMAN, Indianapolis: When Dr. Benson called us concerning this very important study, we were at a loss to know how to comment on his important message because it covers a vast surgical territory. Dr. E. J. Berman and I wondered whether there are any truly asymptomatic abdominal masses in infants and children, and whether any normal or abnormal tumor should be ignored. Our own experience must parallel that of many of our members and guests in the surprising numbers of so-called displaced normal organs in infancy which are in fact gross abnormalities that cannot be identified accurately without an exploratory operation. We have felt that we should call attention to one symptomless abdominal mass, the choledochal cyst, which we have observed in five infants, varying in age from 12 weeks to 2 years. Three were girls and two were boys. Although it is stated by most authorities that 90% of these cysts are accompanied by jaundice and pain, this has not been our experience in the five instances we are reporting. The tumors were very large and apparently without detectable symptoms. Thus, one is not surprised if at surgery a probe may be passed from the cyst to the duodenum, as described by Weber, and if one finds that the biliary tree, including the cystic duct and gallbladder proximal to the cyst, is entirely normal. The precise ex-

planation of the formation of choledochal cyst remains as much a mystery as does the cause of megacolon in Hirschsprung's disease, where one would expect cecal dilatation rather than a localized enlargement immediately proximal to the aganglionic segment. We have treated choledochal cysts with cystoduodenostomy with complete satisfaction and without subsequent cholangitis. This procedure theoretically involves the risk of an ascending cholangitis, and therefore many authorities advocate a routine Roux en-Y type of anastomosis. However, some of these same authorities are strong advocates of thorough sphincterotomy of the ampulla for recurrent pancreatitis, or even common-duct stones, where reflux may also take place. We should like to ask Dr. Benson for his observations as to the cause and treatment of choledochal cysts, and whether there are any truly asymptomatic abnormal tumors that are best treated by ignoring them.

Dr. Willis J. Potts, Chicago: The commonest and most unpredictable tumor in the abdomen in children is neuroblastoma. It is one of the odd malignancies which can flare up in a burst of metastases or can disappear spontaneously with or without treatment. We have had a considerable number of patients with neuroblastoma, but I want to tell you briefly about three cases which illustrate that the condition is by no means always hopeless. The first child, seen about 12 years ago, was 9 months old upon admission to the Children's Memorial Hospital. He had a huge, widespread tumor in the retroperitoneal space. Removal was impossible. A biopsy was done. Microscopically, the cells were fast-growing, undifferentiated, and malignant. I made a grevious error in telling the mother that the outlook was very dim but that x-ray therapy should at least be tried. The tumor literally melted away, and today the child is well. The second case is unique in our experience. Almost six years ago an 18-month-old boy with a tumor about 4 in. in diameter and an inch thick on the back of his neck was admitted to the hospital. The tumor was removed and proved to be a typical neuroblastoma. More thorough examination brought to light a similar tumor under the skin in the lower left quadrant. A calcified mass in the retroperitoneal space was found roentgenographically. No further surgery was performed. The child was given x-ray therapy to the back of the neck and to the abdomen. The tumor in the left lower quadrant disappeared. A few months later a bulge appeared on the head, and x-ray films of the skull showed unmistakable metastases to the bone. A course of roentgen therapy was given to the skull. The child is well today, almost six years following discovery of the tumor, and is apparently free from any sign of new growth. The third case was that of a 2-year-old child operated upon in Milwaukee approximately one year ago for an obstructing mass in the hollow of the pelvis. The tumor could not be removed. Biopsy proved the tumor to be a neuroblastoma. The child was given 2,500 r to the pelvic region. About six months later we were asked to operate again upon this child. We could not remove the tumor either, of course. Biopsy studies at this time showed a tremendous change in the character of the cells. They now resembled those of a neurofibroma. Roentgen therapy, 1,500 r, was given immediately after the second operation. The child was examined recently, and no tumor could be felt. These are a few of the unusual and fortunate cases which have responded to biopsy and roentgen therapy. Cure by biopsy is not spoken as a pleasantry; some children with neuroblastoma get well after biopsy alone. Mechlorethamine hydrochloride (nitrogen mustard) has been advised for the treatment of metastases of neuroblastoma. We have had little success with it; in fact, we are inclined to think that a nice, meaty Oscar Mayer Yellow Brand wiener with plenty of mustard on it taken by mouth is just as effective. The children like it much better.

Dr. Edwin M. Miller, Chicago: I arise not to add anything of real value to the discussion but merely to cite one case which strikingly illustrates the point brought out by Dr. Benson. The patient was a little girl about 3 years old and apparently perfectly well. The mother, who was a very intelligent woman, was bathing her one evening and just happened to notice a rounded swelling on the left side of the child's abdomen. She became alarmed and called her physician, who saw her that night and sent her into the hospital. In spite of her lack of symptoms, a Wilms' tumor was suspected, and x-ray studies showed not only marked displacement of the descending colon but absence of dye in the left kidney pelvis. At operation a very large Wilms' tumor was successfully removed, and examination by the pathologist revealed almost complete destruction of the kidney. The tumor was at one point projecting into the lumen of the renal vein. It was amazing to find such extensive pathology unaccompanied by any clinical symptoms.

Dr. Clifford D. Benson, Detroit: I want to thank Drs. Snyder, Berman, Potts, and Miller for their remarks.

Certainly, I think this group is a narrow one. As Dr. Snyder brought out, if one were to study all the abdominal tumors in children who enter children's hospitals, one certainly would find more malignant than benign tumors. In other words, this is a very small group of children picked up by pediatricians as having asymptomatic tumors. I believe that selection accounts for the number of benign tumors. As far as choledochal cyst is concerned, I think most surgeons interested in pediatric surgery would prefer to do what Dr. Berman has advocated, that is, perform a side-to-side anastomosis in these large choledochal cysts. Occasionally one can remove them, but certainly it is asking for a lot of trouble when it is not necessary. Furthermore, the results have been very good from just the ordinary side-to-side anastomosis. We have done a Roux en-Y operation only once in any of these patients, and that was for a large cyst that extended well down into the right lower quadrant. We felt there that we would get better drainage than we would with the ordinary side-to-side anastomosis, and that over the long period it would be a better procedure.

Dr. Potts has brought out some very interesting things about the neuroblastomas. Anyone who has had any experience with these tumors realizes that the therapeutic end-results are unpredictable. A few cases have been reported—one by Dr. Ladd, I believe—in which nothing was done and the patient survived without any therapy whatsoever. Therefore, whether it is x-ray therapy that will increase the over-all cure rate over what we are getting at present I don't know. The over-all mortality rate is still high in neuroblastoma. The salvage rate even with excision and radiation is probably somewhere between 15% and 20%; but certainly we should try in all these cases to do everything we can, for the case Dr. Potts described shows what may on the surface be a hopeless situation but may occasionally result in a good recovery.

Vascular Dissemination of Cancer in Children

WILLIAM J. GROVE, M.D.; ALVIN A. WATNE, M.D.; OLGA M. JONASSON, M.D., and STUART S. ROBERTS, M.D., Chicago

Although it is generally believed that malignant tumors in children are associated with a poorer prognosis than are malignancies in adults, the reasons for such an assumption, other than clinical observation, have not been made clear. Vascular dissemination of cancer in children may be of importance in this regard. This study is concerned with that aspect of the vascular dissemination dealing with the carriage of cancer cells in the circulating blood of children, and the occurrence of these cells during an operative procedure.

Historical Review

Since 1869, when Ashworth[1] reported cells in the blood which appeared to be similar to the cells of the patient's multiple malignant skin tumors, several investigators[2-4] have reported "abnormal cells" in the blood stream.

In 1954 Cole, Packard, and Southwick,[5] using the Papanicolaou stain, reported cancer cells in the fluid perfused through the major artery and collected from the vein of a colon specimen containing carcinoma.

Fisher and Turnbull,[6] in 1955, reported tumor cells in the blood of the mesenteric veins in 8 of 25 specimens (32%) of colorectal carcinoma.

Engell[7] (1955) reported tumors cells in the peripheral blood in 10 of 79 patients (13%) with various malignancies during surgery and in 7 of 14 patients (50%) with inoperable carcinoma. He reported no relationship to surgical manipulation.

Moore,[8] in 1957, reported cancer cells in the peripheral blood in 93 of 179 patients (52%), and in the blood draining the tumor site in 60 of 109 patients (55%) with carcinoma.

We,[9] in 1958, reported isolation of cancer cells from the circulating blood in 17% of curable, and 31% of incurable, adult patients with malignancies, and mentioned the role of operative manipulation in the occurrence of these cells.

All of these reports are concerned primarily with cancer cells in the blood of adults with malignancies, and, to our knowledge, no study has been made solely of pediatric patients with malignancies.

Methods

Collection of Blood Samples.—Each 2 ml. sample of heparinized blood is processed immediately. Samples are obtained from peripheral sites, including antecubital, jugular, and femoral veins, or from veins draining the tumor site by a catheter, or by direct needle aspiration of the vein.

Technique of Isolation.—The method, given in detail elsewhere,[9] is based on the fact that many cancer cells are lighter than the formed elements of blood, and can therefore be separated by centrifugal subfractionation. The cancer cells are preserved and stained, using the Papanicolaou technique (Fig. 1). The method is not quantitative, since cancer cells may be lost during the various steps of the procedure.

Results

A total of 20 pediatric patients with malignant tumors were studied. These patients, ranging in age from 5 months to 13 years, were divided into five groups: Wilms' tumor, 3 cases; neuroblastoma, 3 cases; teratocarcinoma, 2 cases; carcinoma of the

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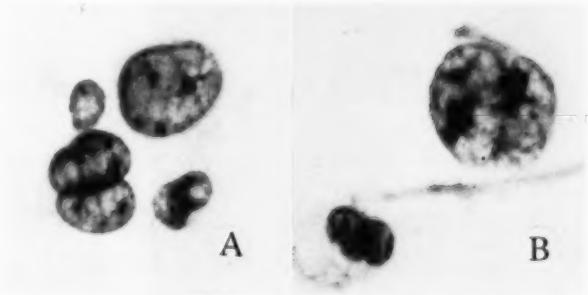

Fig. 1.—*A*, cells isolated from vena cava during surgery in 2-year-old child with Wilms' tumor. *B*, cells isolated from peripheral blood in 5-year-old child with neuroblastoma. Papanicolaou stain; × 700.

thyroid, 2 cases, and various sarcomas, 10 cases (including osteogenic sarcoma of the epididymis, sarcoma of the bladder, mesonephroma of the vagina, fibromyxosarcoma of the thigh, and malignant embryoma of uncertain origin).

Occurrence of Cancer Cells in the Blood.—A summary of the 20 pediatric patients is given in Table 1. Cancer cells were detected in blood samples from 11 of 20 (55%) of the patients, including samples from the antecubital vein, iliac vein, jugular vein, and/or veins draining the tumor site. If only samples drawn from peripheral veins are considered, cancer cells were isolated in 10 of 19 patients (53%), while all of the four blood samples from the tumor site contained cancer cells (Table 2). This total percentage (55) differs markedly from the previously reported [10] total of 47 of 200 adults (24%) with cancer cells in the blood stream, using the same technique.

TABLE 1.—*Summary of Peripheral Blood Findings in Twenty Children with Tumors*

	No.	Positive
Wilms' tumor	3	3
Neuroblastoma	3	1
Teratocarcinoma	2	2
Carcinoma of thyroid	2	1
Sarcomas	10	4
	20	11, or 55%

A correlation of positive blood samples with microscopic blood-vessel invasion is given in Table 3. Although the total number of patients with positive blood samples

TABLE 2.—*Comparison of Peripheral vs. Tumor-Site Blood*

	Peripheral		Tumor Site	
	No.	Positive	No.	Positive
Wilms' tumor	2	2	2	2
Neuroblastoma	3	1	0	0
Teratocarcinoma	2	2	2	2
Carcinoma of thyroid	2	1	0	0
Sarcomas	10	4	0	0
	19 *	10, or 53%	4	4, or 100%

* A peripheral-blood sample was not secured from one patient with Wilms' tumor.

(11 of 20) is comparable to the total number exhibiting vessel invasion (9 of 20), 3 patients with positive blood samples (including a teratocarcinoma, a Ewing sarcoma, and a lymphosarcoma of the anus) had no evidence of blood-vessel invasion. On the other hand, two patients with negative blood samples (a neuroblastoma and a carcinoma

TABLE 3.—*Correlation of Positive Blood Samples with Vein Invasion*

	No.	Positive Blood	Vein Invasion
Wilms' tumor	3	3	2 *
Neuroblastoma	3	1	2
Teratocarcinoma	2	2	1
Carcinoma of thyroid	2	1	2
Sarcomas	10	4	2 †
Total	20	11	9

* One patient with Wilms' tumor had no biopsy. Death occurred at home three months after tumor cells had been found in the peripheral blood.

† One patient with malignant embryoma had a positive biopsy of a metastatic lesion in the liver; no biopsy of primary tumor was done.

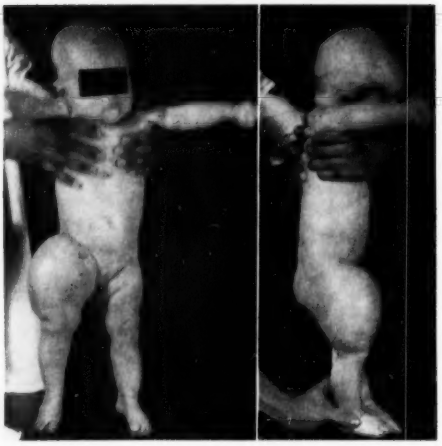

Fig. 2.—Five-month-old infant with fibromyxosarcoma of right thigh. Tumor cells were found in blood sample taken from jugular vein.

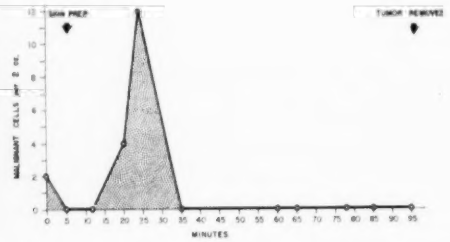

Fig. 3.—Number of cancer cells isolated from peripheral blood during resection of soft-tissue tumor in child shown in Figure 1.

of the thyroid) had microscopic evidence of vessel invasion.

Response to Surgery.—A patient from whom cancer cells were isolated from the peripheral blood preoperatively was studied with serial blood samples during the operative procedure to evaluate the role of operative manipulation. Although the method is not quantitative, as mentioned above, all samples are processed in an identical manner and are therefore comparable.

This patient was born with a soft-tissue mass on the anterior lateral aspect of the right thigh (Fig. 2). A biopsy specimen of this mass taken at 4 weeks of age was interpreted as fibromyxosarcoma, and the patient was given x-ray therapy. Because of the lack of response to this treatment, the child was referred to the University of Illinois Research and Educational Hospitals at the age of 5 months. Tumor cells were isolated from a peripheral blood sample taken from the external jugular vein. In an attempt to obtain blood samples from veins draining the tumor site, a polyethylene catheter was inserted by cut-down through the greater saphenous vein into the left iliac vein, but could not be passed farther. Blood samples were drawn at frequent intervals during the operation. As seen in Figure 3, a shower of cancer cells occurred early in the procedure during dissection over the tumor, although several blood samples drawn during manipulation later did not contain cancer cells. The isolated shower of cells is different from the pattern we have reported previously,[9] in which cancer cells were present in all samples during the operation until the vein draining the tumor was clamped or the tumor was removed (e. g., clamping the renal pedicle, removal of the breast, etc.). An explanation for this difference may be that the volume and number of samples that can be obtained from infants must necessarily be smaller than can be secured from adults.

Summary

Cancer cells were isolated from the circulating blood of 11 of 20 pediatric patients (55%) with malignancies, an incidence approximately two times as great as that reported in a series of 200 adults with malignancies.

Blood-vessel invasion, histologically demonstrated, was present in 9 of the 11 patients having circulating tumor cells.

During resection of a soft-tissue sarcoma, in an infant, a sixfold increase in the number of circulating cancer cells in the peripheral blood was demonstrated.

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REFERENCES

1. Ashworth, T. R.: A Case of Cancer in Which Cells Similar to Those in the Tumours Were Seen in the Blood After Death, Australian M. J. 14:146, 1869.

2. Schleip, K.: Zur Diagnose von Knochenmarkstumoren aus dem Blutbefunde, Ztschr. klin. Med. 59:261, 1906.

3. Aschoff, L.: Ein Fall von Myelom, München. med. Wchnschr. 53:337, 1906.

4. Ward, G. R.: The Blood in Cancer with Bone Metastases, Lancet 1:676, 1913.

5. Cole, W. H.; Packard, D., and Southwick, H. W.: Carcinoma of the Colon with Special Reference to Prevention of Recurrence, J. A. M. A. 155:1549, 1954.

6. Fisher, E. R., and Turnbull, R. B., Jr.: The Cytologic Demonstration and Significance of Tumor Cells in the Mesenteric Venous Blood in Patients with Colorectal Carcinoma, Surg. Gynec. & Obst. 100:102, 1955.

7. Engell, H. C.: Cancer Cells in the Circulating Blood, Acta chir. scandinav., Supp. 201, 1955.

8. Moore, G. E.; Sandberg, A., and Schubarg, J. R.: Clinical and Experimental Observations of the Occurrence and Fate of Tumor Cells in the Blood Stream, Ann. Surg. 146:580, 1957.

9. Roberts, S.; Watne, A.; McGrath, R.; McGrew, E., and Cole, W. H.: Technique and Results of Isolation of Cancer Cells from the Circulating Blood, A. M. A. Arch. Surg. 76:334, 1958.

10. Roberts, S. S.; Watne, A.; McGrath, R.; McGrew, E., and Cole, W. H.: The Response of Cancer Cells in the Circulating Blood to Surgical Stress and Chemotherapy, S. Forum, to be published.

DISCUSSION

DR. FREDERIC WILLIAM TAYLOR, Indianapolis: I feel this paper is too great a contribution to go without discussion. It indicates a change in our entire concept of the disease, particularly that in children. There are certain features that bother us about this whole matter. My colleagues and I, too, have been interested in finding these cells in the peripheral circulating blood of cancer patients. We, like others, would like a little more proof that they are cancer cells. We think they are, but, at the same time, a man-made metastasis would convince us a lot more than any number of morphological descriptions of these cells, or pictures of them. We have taken these cells from the peripheral blood and reinjected them into the patient from whom they were drawn. So far we have been unable to reproduce a tumor. I realize that this does not mean these are not tumor cells. I think they are. Dr. George Moore has grown these cells in vitro. We have never tried that; apparently it is quite a job. Dr. Moore's cultures died out after a short time. Another thing that bothers us is this: Here are tumor cells which we see circulating in the peripheral blood, and they are all good healthy cells, well preserved. Why don't we see some of the cells that are dying? Certainly, most go through the peripheral capillaries and do not form metastases, and yet we never have identified a degenerating form. These cells in the antecubital vein have been through at least two capillary beds before they reach that site; and if they happen to come from the gastrointestinal tract or from the pancreas, they have been through three capillary beds. What is to keep these cells from circulating several times and going through 6, 8, or 10 capillary beds before they are finally picked up in the smear? I wish we could identify some of the degenerating forms.

DR. WILLIAM J. GROVE, Chicago: I was afraid someone might ask that question. I don't know. Perhaps in a larger series the percentage of positive samples found in children will tend to come down. This is suggested because in our earlier work in adults the percentage we found positive was higher than later. Perhaps this will be true in children when the series is larger. We, too, Dr. Taylor, wonder whether these cells are really tumor cells and whether they are alive. You have already mentioned growing them in tissue culture. In our laboratory Dr. Jonasson extracted the blood of mice that had growing tumors and demonstrated that there were cells by the Papanicolaou method that I have outlined. She injected that blood into the heart of other mice of a similar strain, and those animals developed tumors of the same type as the original tumor, in a sense fulfilling Koch's postulate for tumor in the experimental animal. This information, of course, cannot be transplaced directly to man but is certainly suggestive.

PRESIDENT JAMES BARRETT BROWN, St. Louis: How about the persistence of the cells?

DR. WILLIAM J. GROVE, Chicago: I assume you mean the persistence of cells after removal of the primary tumor. The graph that was shown here demonstrated no persistence whatever. We have many studies in adults which demonstrate that as soon as the tumor is removed the tumor cells disappear from the circulating blood. In a patient with carcinoma of the breast that has had cells preoperatively for many days, it can be shown that during the operation

there may be an increase in the number of cells, perhaps during the preparation of the skin. But as soon as the tumor is removed, the tumor cells disappear from the blood.

PRESIDENT JAMES BARRETT BROWN, St. Louis: Does this have anything to do with the work at Bethesda, in which the control of the primary tumor increases the metastasis? Is there any relation between these two things?

DR. WILLIAM J. GROVE, Chicago: I'm sorry, Dr. Brown, but at this moment I do not know the answer to that question. I wish to thank the discussants for their stimulating remarks.

Exophthalmic Goiter, Thyroidectomy, and Life

ROBERT W. BARTLETT, M.D., St. Louis

Many studies have been made of various thyroid problems; however, I am not aware of any previous attempt to ascertain the long-term therapeutic efficacy of subtotal thyroidectomies performed approximately 30 years ago for toxic diffuse exophthalmic goiter.

Available to us were the case files of Dr. Willard Bartlett Sr. and from them were drawn 100 consecutive cases, in the category just mentioned, in which the patients had undergone thyroidectomy 28 to 34 years ago. For inclusion in the series the thyroid gland had to be of the diffuse hyperplastic toxic variety, and the patient had to exhibit exophthalmos clinically so as to eliminate any possible doubt that we were dealing with true Graves disease in every case.

TABLE 1.—*Thirty-Year Follow-Up of One Hundred Patients with Exophthalmic Toxic Goiter*

	Cases
Complete data obtained	74
Incomplete or no data	26
	100
Total patients traced *	82

* Eighteen of these are known to be dead.

In view of the fact that an urban population so constantly shifts, we feared that it might be impossible to locate after a lapse of 30 years a majority of the persons under study. However, as will be noted in Table 1, after a painstaking search we were rewarded by being able to trace 82 of the original 100 patients and by the obtaining of complete follow-up data on 74 patients. Of the 82 patients traced, 18 are known to be dead.

TABLE 2.—*Data in Seventy-Four Patients with Exophthalmic Goiter*

No. of females	54
No. of males	20
Original age limits of group, yr.	9-43
Average age of group at time of original surgery, yr.	31.7
General health since operation, as reported by patient	
Good	39
Fair	33
Poor	2

Of principal interest in Table 2 are the facts that the average age of the group under study was 31.7 years, as might be expected, and that almost all patients reported their long-term postoperative health to have been good or fair.

Table 3 should be of interest to surgeons, since on first glance it would appear that the so-called "recurrence rate" of 14.9% was too high, especially for one recognized as a capable thyroid surgeon. It must be remembered, however, that these patients were operated upon in the period 1924-1930, at which time the patients with Graves disease were a much sicker group preoperatively than today, both because of delay in diagnosis and because of less satisfactory preparation for operation, strong iodine solution

TABLE 3.—*Data on Reoperations*

Reoperation advised	11 (14.9%)
Subsequent treatment	
Reoperation	9
Extensive radium therapy	1
Refused	1
Reasons for reoperation rate	
Hyperthyroidism frequently severer than seen today	
Strong iodine solution U. S. P. (Lugol's solution) only	
Less radical thyroidectomy	

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Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 20, 1958.

U. S. P. (Lugol's solution) only being employed. The net result was a more rapidly performed and less radical subtotal thyroidectomy than that of today, and consequently more frequent "recurrence." My own view for many years has been that the so-called "recurrence" in most instances represented persistence of symptoms due to an inadequate primary operation.

TABLE 4.—*Number of Children Born to Patients and Weight Status*

Married patients	65
Total no. of children	110 (1.7 average per patient)
Children born since operation	41 (0.63 average per patient)
Average preoperative weight, lb.	126
Average lowest postoperative weight, lb.	127
Average highest postoperative weight, lb.	158

The data in Table 4 regarding the number of offspring and the pre- and postoperative weights, are not remarkable.

Of considerable interest to us is the fact that among the 74 cases in which complete follow-up data were obtained there was only one instance of cancer. This was a carcinoma of the breast with extensive axillary metastases, on which we operated, with the patient remaining well the past 20 years. Can it be that toxic goiter inhibits to some extent the later development of cancer? I wonder what the experience of others has been in this regard.

As seen in Table 5, it is noteworthy that of the known causes of death, cerebral vascular accidents accounted for two only. I shall refer back to this point shortly.

Table 6 records postoperative "heart trouble," which was reported in only 7 out

TABLE 5.—*Causes of Death in Eighteen of Eighty-Two Traced Cases*

Hypoparathyroid tetany	1
Cirrhosis	2
Cerebral vascular accidents	2
Severe trauma	3
Cardiac	3
Unknown	7

TABLE 6.—*Patients with "Heart Trouble"*

Patient		Years Postoperative
1	Living at age 74	30
2	Living at age 69	30
3	Living at age 62	29
4	Living at age 68	24
5	Dead, age 60	20
6	Dead, age 62	22
7	Dead, age 73	21 *

* Decompensation.

of the 74 cases, with only 3 cardiac deaths. To us this is indicative of the falsity of the belief that thyroidectomy does not cure exophthalmic goiter but only ameliorates the symptoms.

Although 54 of the 74 patients were women, there were only 2 cases of cholecystitis, whereas approximately 12% of the general adult female population have symptomatic gallstones. Furthermore, the relatively few strokes and myocardial infarcts indicate that there were few obstructions of the coronary, cerebral, and internal carotid arteries. Perhaps additional clues to the genesis both of arterial obstructions and of gallstones might be gained by a more extensive study of the lives of persons who have had or do have diffuse hyperplastic goiter.

TABLE 7.—*Life Expectancy in Persons with Exophthalmic Goiter*

No. of traced patients dead	18
Cause and date of death known	15
Mean age of these 15, yr.	58.7
Mean age of these 18, yr.	56.5
Mean age of known living, yr.	60.2
Calculated mean age of 100 cases, yr.	54

Finally, we come to the question of life expectancy in exophthalmic goiter and find substantiation for certain conclusions which we have long held as valid. As will be seen in Table 7, 18 of the 82 traced patients are now dead. The cause and date of death are known for 15. These 15 patients lived to have a mean age of 58.7 years. The mean age of all 18 patients who died, assuming the date of death of the 3 "unknowns" as

the last day they were seen or heard from, was 56.5 years. The calculated mean age of the original 100 patients, assuming that the 18 untraced patients died upon the day they were last seen or heard from, is 54 years. We are able to conclude from our analysis that the life expectancy of persons having exophthalmic goiter who are treated by subtotal thyroidectomy is as long as that of the general population, as based on life insurance company figures.

Dr. Carl Moyer gave constructive criticism and aid in the analysis of the data involved in this study.

The Doctors Building, Suite 500, W. Pine St. and Euclid Ave. (8).

DISCUSSION

DR. EDWARD JUDD, Rochester, Minn.: We here locally are interested to see that other surgeons have not abandoned completely the treatment of exophthalmic goiter by surgical means. We feel that there is still a certain well-described place for surgery in the tratment of some of these patients, especially young people, children, and young women who are in their active childbearing and menstrual years, to whom we would be loath to administer large doses of radioactive iodine. Of course, it is to be admitted that the endocrine departments have taken over a large share of the treatment of exophthalmic goiter. In certain other very urgent situations, even in older people, however, we do not hesitate to proceed at once with a radical subtotal thyroidectomy, for example, in patients who are suffering from carcinoma elsewhere in the body demanding early surgical intervention, and other situations of that type. Also, as Dr. Bartlett suggested, there are some cases in which the diagnosis is not absolutely certain; you will recall that they encountered a malignant condition in one of their cases. More particularly in regard to the thyroid gland, we are not always positive that we are dealing only with exophthalmic goiter. The late Dr. Henry Plummer used to stress with us the fact that the disease runs a very typical life cycle; that is, it runs between "peaks" and "valleys." It would appear that here at present, just as in St. Louis, we are in one of the valleys. The present disease seems to be of a very mild form. We are not seeing so much of it, and it seems to be relatively easy to handle. It would appear that at the time of Dr. Bartlett's father's activity the disease in St. Louis was a very vicious one, just as it was elsewhere in the United States. Whether we are going to get back to one of the peaks Dr. Plummer talked about in other years will be very interesting to see.

Dr. Bartlett points out the extreme importance of a long-term follow-up. We do not know of any other studies that encompass a 30-year follow-up. It is very difficult to try to follow any patient for 30 years; you all know that. Dr. Bartlett is to be congratulated on bringing to us this very worth-while information. All of us have heard various exponents of one type of treatment or another for exophthalmic goiter point out that the patient seems to be "cured" after three or four years. We all are aware of persons who have gone through a stage of myxedema after radical subtotal thyroidectomy and who, as long as 30 years later, may have a recurrence of their original exophthalmic goiter. If there is one message that Dr. Bartlett brings to us, it is certainly that of the need of a prolonged follow-up study before any final conclusion can be drawn. We are in the habit of citing our postoperative recurrence rate of about 5%. Perhaps if we had a 30-year follow-up for all of our cases, we would be a little shocked to see what the recurrence rate actually is. Finally, in regard to those other conditions the body falls heir to, and their interesting implications Dr. Bartlett suggests we all reflect upon, I am not prepared at the present moment to make any definite statement.

DR. ROBERT W. BARTLETT, St. Louis: I was very much interested in Dr. Judd's suggestion that perhaps exophthalmic goiter was a more vicious disease 30 years ago than it is today. I had always assumed that at that time the general practitioners and some of the internists were treating the symptoms of nervousness and overactive heart without recognizing the true nature of the disease until much later, by which time the patient had become pretty well emaciated.

Place of Radical Neck Surgery in Thyroid Carcinoma

MELVIN A. BLOCK, M.D.; J. MARTIN MILLER, M.D., and BROCK E. BRUSH, M.D., Detroit

When the diagnosis of carcinoma of the thyroid gland is established, the decision must be made whether or not to perform a neck dissection. Although our experience does not justify a final answer with respect to this question, we believe it does indicate the necessity for a radical neck dissection for patients with evidence of cervical lymph node metastases from an operable carcinoma of the thyroid. The data do not indicate the absolute necessity for an immediate neck dissection for patients without cervical lymphadenopathy in whom thyroid carcinoma is present. However, we do believe that a modified neck dissection is justified in many of these patients.

Materials

The microscopic diagnosis of carcinoma of the thyroid has been made on 132 cases occurring through 1957 at the Henry Ford Hospital. The first patient was seen in 1924. Of the total of 132 patients, a neck dissection was performed on a total of 59 patients, who serve as the basis for the primary considerations of this report. A total of 92 patients have been followed for three or more years. Sixteen of the patients have died of carcinoma of the thyroid, one death being an operative death (Table 1). Massive local or widespread metastatic disease was present in 12 patients on their initial visit. Of the total of 132 patients, 80 have been followed for at least three years after definitive thyroid surgery, and, of these, 52 patients have been followed for five or more years after definitive thyroid surgery (Table 2). A neck dissection was performed at the time of thyroid surgery or soon thereafter on 24 of the group followed at least three years. A neck dissection was carried out at a later date on three additional patients.

TABLE 1.—*Patients with Carcinoma of the Thyroid Followed Three or More Years, 1924-1957*

Total no. patients followed 3 yr.	92
Massive local or metastatic disease initially	12
Deaths from thyroid carcinoma (1 operative)	16

TABLE 2.—*Patients Followed Three and Five Years After Definitive Surgery for Thyroid Carcinoma*

	Three Years	Five Years
No neck dissection	53	38
Immediate neck dissection	24	12
Late neck dissection	3	2
Total	80	52

The patients have not been grouped according to a microscopic classification of thyroid carcinoma in this study. The clinical evidence of the extent of the disease has appeared to be of greater importance in our surgical management of individual patients. Even papillary carcinoma of the thyroid varies greatly in its malignant characteristics clinically in different patients. We have seen cervical lymph node metastases in a number of patients with predominantly follicular carcinoma. Both follicular and papillary varieties of thyroid carcinoma frequently coexist. Meissner, Colcock, and Achenbach[1] were able to find no consistently reliable factor that the pathologist could use to predict whether or not cervical lymph node metastases are likely to be present. Knowledge of the microscopic variety of thyroid carcinoma is of value in determining the prognosis, however.

No pathologic studies were used other than those employed routinely by the department of pathology in our institution.

Results

Frequency of Node Metastases in Patients With and Without Cervical Lymphadenopathy.—A total of 59 neck dissections were carried out in patients with carcinoma of the thyroid (Tables 3 and 4). The physical examination form in use at the Henry Ford Hospital is composed so that the presence or absence of cervical lymphadenopathy is always indicated. The patients included in

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Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 20, 1958.

TABLE 3.—*Frequency of Node Metastases Found in Lateral Neck Dissections for Thyroid Carcinoma*

Cervical nodes not palpable		26
Nodes negative	18	
Nodes positive	8 (31%)	
Neck dissection immediate	6	
Neck dissection later because of lymphadenopathy (3, 7 yr.)	2	
Cervical nodes palpable		33
Biopsy cervical node first evidence of thyroid Ca	22	
Neck dissection done with thyroid surgery	11	
Nodes negative	2	
Nodes positive	9	
Total		59

TABLE 4.—*Frequency of Node Metastases Found in Lateral Neck Dissections for Thyroid Carcinoma*

	Total	Negative Nodes	Positive Nodes
Cervical nodes not palpable	26	18	8 (31%)
Cervical nodes palpable	33	2	31 (94%)
Totals	59	20	39 (67%)

this study were always examined by several physicians. If the presence of palpable lymph nodes was noted by any examiner, the patient was placed in the group of preoperative cervical lymphadenopathy for purposes of this evaluation.

In 26 of the 59 patients cervical nodes were not palpable preoperatively. In 8 of the 26 patients, or 31%, the microscopic examination of the cervical nodes disclosed the presence of metastases. However, in two of the patients the neck dissection was not carried out until three and seven years, respectively, following the original thyroid surgery for malignancy. An immediate neck dissection was not done because of the absence of cervical lymphadenopathy in these two patients, but the neck dissection was performed later, when palpable cervical nodes appeared.

In 33 of the 59 patients on whom a neck dissection was done, palpable cervical lymphadenopathy was present prior to the thyroid surgery. In 31 of these 33 patients, or 94%, metastases to the nodes were demonstrated by the pathologists. It is of interest that in 22 of these 33 patients cervical lymphadenopathy was the first clinical indication of thyroid malignancy, and a biopsy of a cervical lymph node was the first operative procedure carried out (Table 3).

Three- and Five-Year Follow-Up.—Three- and five-year follow-up data are recorded in Tables 5 and 6. Six patients still living after surgery for thyroid carcinoma required further therapy at a later date for cervical metastases. One operative death occurred in 1928. Five patients are alive with metastatic disease, and 15 patients have died of thyroid carcinoma. However, in 10 of these 15 patients the tumors were inoperable when the patients first were seen because of the presence of extensive malignancy.

Three-Year Follow-Up After Thyroid Surgery on Patients with Cervical Lymphadenopathy.—A total of 19 patients with palpable lymphadenopathy underwent surgery for cure of thyroid carcinoma and were followed at least three years (Table 7). None of these patients had clinical evidence of spread of the malignancy elsewhere except for the presence of cervical lymphadenopathy. A neck dissection was carried out in

TABLE 5.—*Patients with Thyroid Carcinoma Living Three and Five Years After Surgery: Follow-Up Data*

	Three Years	Five Years
Living and well — no further therapy	57	32
Treatment later for local recurrence	1	1
Treatment later for cervical node metastases	6	5
Living with distant metastases	5	3
Total	69	41

TABLE 6.—*Cause of Deaths in Patients with Thyroid Carcinoma Followed at Least Three Years*

	Number Patients
Other causes	7
Operative	1
Thyroid carcinoma	15
Extensive Ca initially, inoperable	10
Distant metastases initially	3
Thyroid surgery done for cure	2

TABLE 7.—*Thyroid Carcinoma: Three-Year Follow-Up After Definitive Thyroid Surgery on Patients with Cervical Lymphadenopathy*

	No Neck Dissection	Neck Dissection
Living and well — no further Rx	3	8
Neck recurrence requiring more Rx	4	0
Living with distant metastases	0	1
Died of unrelated cause	1	1
Died of thyroid carcinoma	1	0
Total	9	10

10 of these patients, but not in 9 patients. Four patients of the nine who did not have a neck dissection later required further therapy for cervical metastases, and an additional patient died of distant metastases from thyroid carcinoma. None of the patients on whom a neck dissection was done had further difficulty with cervical metastases, and none have succumbed to the disease, although one is living with evidence of distant metastases.

Although the total number of patients in these groups is small, this evidence strongly indicates the advisability of performing a neck dissection in patients with palpable cervical lymphadenopathy who have an operable carcinoma of the thyroid.

Three-Year Follow-Up After Thyroid Surgery on Patients Without Cervical Lymphadenopathy.—A total of 59 patients without palpable cervical lymphadenopathy underwent surgery for cure of thyroid carcinoma and have been followed for at least three years (Table 8). In 2 of 14 patients on whom a neck dissection was done immediately, metastases to the nodes were found after microscopic study. These 14 patients have had no further difficulty, and all are living and well.

TABLE 8.—*Thyroid Carcinoma: Three-Year Follow-Up After Definitive Thyroid Surgery on Patients Without Cervical Lymphadenopathy*

	Number Patients
Neck dissection done	14
Nodes negative	12
Nodes positive (surgery immediate)	2 *
No neck dissection	45
No evidence further difficulty	31
Cervical node metastases later	3 *
Local recurrence later	2
Living, with distant metastases	2
Death, postoperative	1
Death, unrelated cause	5
Death, carcinoma thyroid (cervical node metastases)	1 *
Total	59

* Total, six patients with known cervical node metastases.

Of the 45 patients for whom an immediate neck dissection was not carried out, 4 were later found to have cervical metastases. One of these four patients died of thyroid carcinoma. This patient was seen in 1936, with the finding of a nodular thyroid gland and no palpable cervical lymph nodes. A bilateral subtotal lobectomy was performed, the pathologic study showing the presence of an area of solid adenocarcinoma. In 1944 the patient finally permitted removal of the remaining thyroid tissue, which was reported by the pathologists to be free of carcinoma. Death occurred in 1946, of widespread metastatic carcinoma to cervical nodes, mediastinal nodes, lungs, and bone.

Thus, at least 6 of the total of 59 patients (10%) were found to have cervical node metastases. In four of the six patients the cervical node metastases became evident clinically at a later date after the original thyroid surgery.

Comment

Surgery directed against carcinoma of the thyroid has changed greatly in the past 25 years. In earlier years carcinoma of the thyroid was frequently not diagnosed and treated until it was extensive and in a late stage. The surgery consisted usually of a partial lobectomy and obviously was inadequate local treatment for carcinoma of the thyroid gland. This experience demonstrated the necessity for earlier recognition and treatment of the disease, even though it is not a common type of malignancy. It also showed that total lobectomy should be the minimal definitive surgical procedure for carcinoma involving a lobe of the thyroid.

A large proportion of thyroid operations carried out currently are for removal of

thyroid nodules, and carcinoma of this gland is being diagnosed and removed in earlier stages. Thyroid carcinoma is being removed oftener in patients who do not have palpable cervical lymph nodes. However, the extent of surgery which is necessary is still a problem. Since data of earlier years are not applicable, and since long follow-up periods for this type of malignancy are required, available experience is not of great help in answering this question.[2,3]

This discussion is limited primarily to the problem of when neck dissection should be carried out for thyroid carcinoma. This question cannot be settled with finality, for our data are not sufficient in numbers of patients or in duration of follow-up to permit a valid statistical analysis. It is wise, however, to review experience from time to time, since some guidance for future conduct is obtained.

The data do indicate definitely the advisability of performing a neck dissection if palpable cervical lymphadenopathy is present in a patient with an operable thyroid malignancy. Nearly all of these patients do have metastases to the nodes. If only one or a group of nodes containing metastases from thyroid carcinoma is removed, many patients have further difficulty with node metastases, in our experience (four out of nine patients, Table 7).

A decisive answer with respect to the advisability of neck dissection in patients without palpable cervical lymph nodes is not possible from our data. In our experience, at least 30% of these patients have been found to have metastases to cervical nodes. It appears that if neck dissections are not done for this group, at least 10% (4 out of 45 patients, as shown in Table 8) will develop clinical difficulty, with cervical node metastases. One patient in this category died of thyroid carcinoma 10 years after appearance of the initial thyroid carcinoma. Thus, perhaps 1% to 2% of patients with thyroid carcinoma without palpable cervical lymphadenopathy and without evidence of distant metastases will die of thyroid carcinoma if no surgery other than lobectomy is carried out (Chart).

The *Outlook for Patients Without Cervical Lymphadenopathy After Surgical Removal of Primary Lesion of Thyroid Carcinoma*

Localized Thyroid Carcinoma
Cervical Nodes Not Palpable
Primary Lesion Removed

At least 10% later have clinical evidence of cervical metastases if no immediate neck dissection

At least 30% have microscopic evidence of cervical node metastases (at time of thyroid surgery or later appearance of cervical lymphadenopathy)

At least 1%-2% die later of thyroid carcinoma if no further therapy is given

There are a number of other considerations relative to the advisability of performing neck dissections for patients with thyroid cancer in whom cervical lymphadenopathy is not found. The operative risk for thyroid or neck surgery is low—well under 1%. Can carcinoma spread from isolated residual cervical node metastases and later kill the patient? It is conceivable that this can occur, but difficult to prove. In our small group, however, nearly as many patients developed evidence of distant metastases as developed cervical metastases (three *vs.* four, Table 8).

Thus, it appears that in evaluating the efficacy of neck dissection for thyroid carcinoma in patients without cervical lymphadenopathy one is counterbalancing small percentages of possible help against small percentages of possible detriment to the patient. The policy followed in clinical practice in such situations usually varies with the surgeon and the patient and will be governed by such factors as the philosophy of the surgeon regarding radical procedures for cancer, the attitude of the patient, the age and condition of the patient, how closely the patient will be followed, and findings at the time of thyroid surgery.

The frequency of metastatic carcinoma in patients without palpable cervical lymphadenopathy in this study (31%) is considerably lower than the figure of 60% or more reported by Frazell and Foote.[4,5] Our figure was not increased much (to 43%) by considering only the definitely papillary lesions. However, McClintock[6] reports that only 8% of his patients have had further difficulty, when only a lobectomy was performed in a patient who had no evidence of metastasis from thyroid carcinoma.

The over-all frequency of cervical lymph node metastases found in our neck dissections was 67%. Thus, if any single arbitrary rule is to be established with respect to neck dissections, it should be to perform this operation. It appears to be better judgment to perform more radical surgery early for malignancy than to reserve it for late stages. In general, surgical procedures carried out for carcinoma of the thyroid in our institution have become more extensive as experience has accumulated over the years.

The technique of performing a radical neck dissection can vary much with respect to the degree of thoroughness and extent. Modifications of the neck dissection have come into use in patients with thyroid carcinoma. We have modified the neck dissection in certain patients by preserving the sternocleidomastoid muscle and by omitting the dissection of the submaxillary gland area. Otherwise the dissection is entirely similar to the classic radical neck dissection and always includes a posterior-triangle dissection and removal of the internal jugular vein and carotid sheath with associated lymph nodes.

Our practice with regard to neck dissections for thyroid carcinoma is outlined in Table 9. We try to individualize the therapy to some extent. A radical neck dissection is carried out for patients with obvious cervical metastases, or a lesion which is locally invasive beyond the thyroid gland and still is operable.

The modified neck dissection has been used for patients without cervical lymphadenopathy found to have unquestionable thyroid carcinoma on frozen-section study at the time of surgery. A modified neck dissection is also carried out in cases without cervical lymphadenopathy in which the frozen-section study was not diagnostic but in which more than a minute area of malignancy was found on microscopic study of fixed sections. The modified neck dissection is carried out in such patients, especially if a second operation is also indicated to complete a total thyroidectomy. As discussed above, we realize that experience to date also justifies less radical policies of surgical therapy in this group of patients without cervical lymphadenopathy.[6] However, the low risk and low morbidity associated with the modified neck dissection also justify this degree of surgery, since it may help a few of these patients. Although removal of the sternocleidomastoid muscle is not severely disfiguring, we believe its preservation does minimize disfigurement and disability and that it is not necessary to remove it in all of these patients. It is possible to complete an adequate dissection of the posterior triangle of the neck and remove the lymph nodes with the internal jugular vein and still preserve the sternocleidomastoid muscle. The submaxillary area has not always been removed, inasmuch as Frazell and Foote[4] report involvement of nodes in this group in only 1.5% of patients without cervical lymphadenopathy.

TABLE 9.—*Indications for Lateral Neck Dissection in Treatment of Carcinoma of Thyroid*

Radical neck dissection
Palpable obvious cervical node metastases
Lesion locally invasive
Lesion locally resectable
Modified neck dissection
Definite thyroid carcinoma in lobe on frozen section; neck nodes not palpable
More than minute area of malignancy on fixed sections; neck nodes not palpable (especially when reoperation is done to complete total thyroidectomy)
Neck dissection not done
Centrally located isthmus malignancy; neck otherwise negative
Minute microscopic focus of carcinoma thyroid found on fixed sections; neck examination negative
Pathologic diagnosis of malignancy questionable
Widespread distant metastases; lateral neck areas negative on examination

Black [7] and Crile [8,9] point out that the nodes immediately adjacent to the thyroid gland are probably involved first by metastases to cervical nodes. This includes nodes immediately superior and inferior to the thyroid gland and the retrothyroid and paratracheal nodes. If the dissection of nodes in the region of the thyroid gland is inadequate, a radical dissection in more lateral areas of the neck does not appear logical.

The lethal nature of each of the microscopic varieties of thyroid carcinoma varies greatly from patient to patient. There are two patients in our group who have had removal of cervical nodes which show metastatic thyroid carcinoma microscopically, but the patients have refused further definitive surgery. Yet these two patients are alive 4 and 10 years, respectively, after the cervical node excisions. On the other hand, patients may develop widespread metastases and die before or within a short time after evidence of thyroid malignancy appears in the neck. Patients die of thyroid carcinoma primarily either from extensive malignancy locally in the region of the thyroid (inoperable when first seen or recurrent after inadequate thyroid surgery), or they die of distant metastases. Thus, neck dissections might be considered of secondary importance as lifesaving measures. There are patients, however, who do have difficulty with the presence of cervical metastases, and it is conceivable that these metastases can contribute to a fatal outcome. This is a principle which has proved valid for other malignancies and should apply also to thyroid carcinoma, even though sometimes less rapid in its progression. It is our opinion, therefore, that carcinoma of the thyroid should be treated with adequate local surgical removal of the primary thyroid lesion, and, in addition, that neck dissections are necessary in certain patients and justified in others.

Summary and Conclusions

A radical neck dissection should be carried out for patients with operable carcinoma of the thyroid and evidence of metastases to cervical nodes.

Approximately 30% of patients with thyroid carcinoma without palpable cervical lymphadenopathy were found to have metastatic carcinoma to the cervical nodes removed by neck dissections at the time of thyroid surgery or at a later date.

Evidence of metastases to cervical nodes will appear later in at least 10% of patients with thyroid carcinoma without palpable cervical lymphadenopathy.

A modified neck dissection appears to be justified for many patients with carcinoma of the thyroid in the absence of palpable cervical lymphadenopathy. Although the data do not dictate the absolute necessity for this procedure, better results are suggested if it is done.

Complete local eradication of thyroid carcinoma is the most important component of the surgical treatment of this disease. This consists of total lobectomy as the minimal procedure, and frequently total thyroidectomy.

Long-term experience with thyroid carcinoma indicates the advisability of a more radical surgical approach in the early stages of the disease. This is in accordance with basic concepts of the surgical therapy of malignancy.

Henry Ford Hospital (Dr. Block).

REFERENCES

1. Meissner, W. A.; Colcock, B. P., and Achenbach, H.: Pathologic Evaluation of Radical Neck Dissection for Carcinoma of the Thyroid Gland, J. Clin. Endocrinol. 15:1432-1436, 1955.

2. Horn, R. C., Jr., and Dull, J. A.: Carcinoma of the Thyroid: A Re-Evaluation, Ann. Surg. 139:35-43, 1954.

3. Horn, R. C.: The Pathologic Physiology of Carcinoma of the Thyroid, S. Clin. North America 35:1669-1681, 1955.

4. Frazell, E. L., and Foote, F. W., Jr.: Papillary Thyroid Carcinoma: Pathological Findings in Cases With and Without Clinical Evidence of Cervical Node Involvement, Cancer 8:1164-1166, 1955.

5. Frazell, E. L., and Foote, F. W.: Papillary Cancer of the Thyroid: A Review of 25 Years of Experience, Cancer 11:895-922, 1958.

6. McClintock, J. C.: An Outline of Treatment for Cancer of the Thyroid Gland, Exhibit, Clinical Meeting of the American College of Surgeons, Chicago, October, 1958.

7. Black, B. M.: Surgical Treatment of Carcinoma of the Thyroid Gland, J. Clin. Endocrinol. 9:1422-1428, 1949.

8. Crile, G., Jr.: Adenoma and Carcinoma of the Thyroid Gland, New England J. Med. 249:585-590, 1953.

9. Crile, G., Jr.: Fallacy of the Conventional Radical Neck Dissection for Papillary Carcinoma of the Thyroid, Ann. Surg. 145:317-320, 1957.

DISCUSSION

Dr. Henry Mason Morfit, Denver: I welcome the opportunity to endorse the scheme outlined in this paper, and I think that in the coming years more of us will come to this line of thinking. It is not a perfect answer to every condition, as indicated by the last slide, showing that when the lesion occurs in the midline, for example, the question is on which side the neck dissection should be done. So the procedure won't answer everything, but I do think it will help in the majority of cases.

Since following this method, it has come as a sort of bounty to us, somewhat unexpectedly, that the patient or the patient's family, once faced with the diagnosis of carcinoma of the thyroid, or, for that matter, cancer in any form occurring throughout the body, always wants to feel that everything is being done to give the patient the best chance of never again hearing from this disease.

Consider for a moment what alternatives are open to the patient who has had a lump removed from the thyroid and has had the incision closed without any further treatment. Such a patient may be advised by one physician to follow the operation with radiation therapy; another physician may tell him to go back and have the whole thyroid taken out; someone else may say: "Have your neck dissection done now." Another may say: "Don't do it now. Don't do it until the nodes show up." Another will say: "Have the whole thyroid taken out and get some I^{131}." I assure you that, regardless of how sincere we physicians may be in arguing and discussing these things among ourselves, in the mind of the patient it all adds up to a group of doctors who don't know what to do. On the contrary, if the physician has followed the diagnosis of carcinoma with removal of the total thyroid gland and, if the lesion was homolateral, with a neck dissection also, then he can honestly face the family and say: "Yes, it was cancer; but we have done everything now that could possibly be done to give your daughter the best chance of never again hearing from it." We have found this to be a very solid argument and a welcome point of view, and one accepted by the patient.

Dr. Claude J. Hunt, Kansas City: Dr. Block and his group are to be congratulated on presenting to us such a timely paper and on the statistics that he has presented, which point very definitely to the fact that cancer of the thyroid should be handled as cancer elsewhere; that is, the lesion should be removed and node-bearing tissue excised at the time of the operation if it is possible to make a frozen-section diagnosis that the lesion is malignant. I admit this has been a very controversial problem, and there have been made excellent and authoritative expressions relative to when a neck dissection should be carried out. There are those who believe that if there is no invasion of the capsule, and if the lesion is apparently confined, and if there are no apparent palpable lymph nodes, it is not necessary at that time (if the lesion is papillary) to remove the lymph-node-bearing area. I approach the problem from the standpoint that the surrounding node-bearing area should be excised whether there are palpable nodes at the time of the original operation or not. This is not a radical procedure, which is rarely indicated.

If the surgeon reviews his records, he will find he has patients coming back to him a few years later with enlarged nodes in the neck on whom he did not do a neck dissection, but simply a lobectomy on that side, with removal of the isthmus. This should be convincing evidence that he should adopt the policy of treating cancer of this area as cancer is handled elsewhere, namely, by removal of the lymph-node-bearing tissue.

I should like to show four slides to illustrate the fact that at the time of the original operation I should have done a neck dissection. [Slide] This was of a boy 7 years of age, who five years later came back with a chain of nodes along the side of the sternocleidomastoid muscle. We then did what we should have done at the first operation, a neck dissection; it has now been three years, and he has no evidence of recurrence. He has had radioiodine-uptake studies, and at the present time they are negative. In another patient on whom I operated,

in 1932, who had a lesion confined to the thyroid, with no apparent involvement of lymph nodes, we did a total lobectomy with removal of the isthmus. Some 11 years later he came back with extensive lymph-node invasion of the side of the neck. We then did a radical dissection, with removal of muscles and internal jugular vein. He should have had the node-bearing tissue removed at the primary operation. After this he had extensive irradiation, which was, I think, too extensive in that it produced tremendous fibrosis of his neck, resulting ultimately in so much constriction of both the trachea and the esophagus that he subsequently had to have a tracheotomy and a gastrostomy for feeding purposes. He in time died. Autopsy showed extensive radiation reaction, with fibrotic constriction of the two important structures. Encapsulated cancer also was present.

[Slide] This shows a boy 11 years of age whose case illustrates the attitude many physicians take toward lumps in the thyroid in young people. To my mind, all such nodules should be removed, and many of them will be found to be malignant at the time of operation. This boy, however, had a lump in the neck and some involved nodes along the side of his neck. It was thought by his local physician that they were due to diseased tonsils, and he had a tonsillectomy. However, he came to us some months later with extensive node metastases on both sides of his neck. We did a bilateral neck dissection of a modified radical type. The muscles were not removed. That was four years ago. Subsequently he had a recurrence of his malignancy in the posterior triangle of the right side of his neck; this growth was removed surgically, and there were five nodes, three of them malignant. This slide shows the extensiveness of the lesion at the time of our primary operation. [Slide] You can see there was a tremendous row of nodes on each side of the neck, extending down into the supraclavicular space, as well as into the upper part of the mediastinum.

[Slide] When we do a bilateral neck dissection, we usually insert a tracheotomy tube because there is a very high incidence of tracheitis that develops after such an extensive procedure. A tube of this type will give the patient a great deal of comfort and will cause no defect in the neck. It prevents labored breathing and fluid accumulation in the bronchi and reduces the possibility of pneumonia. It can be removed in two or three days.

In the ordinary case, when there is a limited amount of lymph-node invasion, I am not sold on the idea of a radical neck dissection. One must individualize each case, and it depends on the nature of the lesion, particularly on the extent of the lymph-node invasion, as to how extensive the neck dissection should be. A local node dissection does not mean a radical neck dissection. Lymph-node extension from thyroid cancer is in four directions: locally; behind the gland in the tracheoesophageal groove; laterally but mesial to the carotid sheath; into the superior mediastinum, supralaryngeal nodes, and the lymphatics along the superior thyroid artery—the only avenue for wide lateral neck dissection. Therefore I think the lymph-node dissection should be confined to these areas, and in such an instance it is not necessary to remove the ribbon muscles or the sternocleidomastoid muscle, an operation which is most undesirable and disfiguring in a young person. If a wider extension is present, surgery will, of course, have to meet the problem as it presents itself. One must remember that most cases of thyroid cancer are curable without radical, disfiguring operations. If no nodes are involved, I think there should be a conservative removal of the adjacent lymph-node-bearing tissue; but if there is extensive involvement, as in this young boy, there should be a more complete neck dissection.

In 100 consecutive cases of nodular goiter and multiple nodular goiter there were 12 cancers. The youngest patient was 7; the oldest, 73, and nine were below the age of 20, indicating strongly that young persons who have nodules in the thyroid gland should have them removed.

Dr. Robert Woodruff, Denver: I realize it is a very controversial question as to whether a lateral neck dissection should be done in a case in which there is no evidence of tumor spread in the neck. However, I should like to say a word in favor of deferring neck dissection in those cases in which no lateral neck spread is demonstrated. If prophylactic neck dissection definitely adds something to the treatment of this disease, it should certainly be carried out at that time; on the other hand, if it does not add anything particularly, I think it should be deferred. True, it is a low-risk procedure; on the other hand, it is slightly deforming, and many of these patients are young girls. Also, some people in whom the spinal accessory nerve is injured have a great deal of discomfort from dropped shoulder.

As we all know, these are very slow-growing lesions, particularly the papillary follicular variety. It amazes me to see that some of the people who suggest that in other tumors of the head and neck we should accept a wait-and-see attitude and not do a neck dissection until we

see definite evidence of metastasis in the neck, will in carcinoma of the thyroid, especially papillary carcinoma, which is very slow growing, advocate going right ahead and doing a prophylactic radical neck dissection. I have a personal series of approximately 25 cases of papillary follicular carcinoma of the thyroid which I have followed up to 15 years. As far as I know (and I have a pretty complete follow-up on most of the cases) the patients are all alive, in spite of the fact that at least one of them has distant metastasis. Moreover, there is other evidence of slow growth in these cases. I have several patients who I know have had metastases in the neck for long periods of time prior to surgical treatment. They have been treated and are well, long after their surgery. One case in particular was that of a girl whom I saw six years after she had had a first biopsy, which was positive for metastatic papillary carcinoma of the thyroid in lymph nodes of the neck. I carried out definitive surgery. It is now 12 years since operation, and she is well and free of tumor, as far as I can ascertain. It is interesting that in most large series of carcinoma of the thyroid, at least of the papillary and follicular type, practically all of the deaths reported are due to recurrence in the neck, and not to distant metastases. It therefore seems reasonable to me to defer radical neck dissection until the time when we get a little evidence of spread in the neck. There is pretty good evidence to show that the distant spread of carcinoma of the thyroid is not through the lymph nodes but through vascular spread.

One further point in closing: In many of these cases the first metastasis is on the opposite side of the neck, and under the sternum, in those areas which we do not reach with the ordinary dissection.

DR. VICTOR E. CHESKY, Halstead, Kan.: In the main I heartily agree with what the authors have said. There has been considerable difference of opinion as to radical neck dissection. I think the disagreement arises mainly from the difference in the classification of "malignant thyroid." I agree with the last speaker in that I do not do radical neck dissection in all cases of malignant thyroids. Graham, a number of years ago, classified the solitary adenomas as "malignant" and "nonmalignant," depending upon whether there was invasion of the capsule or of the blood vessels adjacent to the capsule.

According to our experience, thyroid carcinoma is among our lowest-grade malignancies. We have operated on a number of these patients who had either invasion of the capsule or invasion of the capsule and adjacent blood vessels, by doing a total lobectomy for removal of the isthmus and pyramidal lobe, and we have followed them for a number of years—some of them as long as 14 years. We have had no recurrence so far in at least 90% of those cases. Of course, we can't say that some of the later cases might not have recurrence, but we have followed a number of them for 14 or 15 years without any sign of recurrence. Almost everyone agrees that solitary adenomas of the thyroid should be removed because of their tendency to become malignant. To diagnose malignancy before surgery is often impossible, the diagnosis usually being made by the pathologist. If there are no palpable lymph nodes in the neck, even though the blood vessels in the capsule are invaded, we do a total lobectomy, with removal of the isthmus, without a radical neck dissection.

DR. BROCK E. BRUSH, Detroit: We have taken the position that while cancer of the thyroid is a slow-growing tumor in many instances, it still is cancer and should be treated as such. We feel that if a neck dissection is deferred, these patients will often be lost; some of them, in our experience, have come back when the disase has spread greatly, and they have nodes that are very extensively involved. We believe these patients would have been much better treated by neck dissection at the time the original cancer was found.

A good local excision of the cancer, as Dr. Chesky has said, and with whom I am sure we all agree, a total lobectomy and excision of the nodes in that area, is the first thing to do; but in patients who have a very definite carcinoma a radical neck dissection is indicated, for as you have seen, 30% of these patients will be found to have metastatic nodes when the neck dissection is done and the specimen is examined by the pathologist. This number we feel is very large; and it seems to me, at least, that it is wise to do a definitive operation at the time, rather than wait for the metastasis to show up and then have a difficult job on one's hands. It is not always possible to follow these patients closely, and very often they do not come back when they have one little node that they can feel or that becomes noticeable. We have seen too many of them who have come back when they had very extensive cervical node metastases. It seems to us that cancer of the thyroid is still cancer and should be treated as such, with good local excision and then excision of the node-bearing area.

Dr. Melvin A. Block, Detroit: This is, of course, a controversial subject, especially as pertains to neck dissections for the patients without palpable cervical lymphadenopathy. We also have tried to individualize therapy for the patients and do not carry out neck dissection for all patients, as was discussed in the paper. Our attitude, however, has increasingly been that of performing more radical surgery in the early stages of the disease, rather than of reserving radical operation for late stages of the malignancy.

May I also point out the importance of removing the nodes in the vicinity of the thyroid gland, i. e., those just superior and inferior to the gland and along the tracheoesophageal area, near the thyroid gland.

Pulmonary Resection for Metastatic Tumors

HAROLD C. HABEIN Jr., M.D.; O. THERON CLAGETT, M.D., and JOHN R. McDONALD, M.D., Rochester, Minn.

In 1950, Seiler and associates [1] reported on 10 patients on whom pulmonary resection had been carried out at the Mayo Clinic in an attempt to eradicate metastatic tumors of the lungs. Hood and co-workers,[2] in 1955, added 33 more patients to the series. One of the latter series was excluded later because what was considered earlier as a metastatic ovarian carcinoma is now believed to have been a second primary tumor (alveolar-cell carcinoma). The current study is an extension and continuation of the two previous ones. Its purpose is to bring the material up to date by presenting information on more recently treated patients and later follow-up data on the previous patients. By this means it is hoped to assess further the status of resection in the treatment of metastatic malignant pulmonary lesions.

General Data in Present Study

By the end of 1956, a total of 96 patients had undergone pulmonary resection at the Clinic for metastatic malignant tumors; the first procedure of this nature was done here in 1941. The series does not include patients in whom only biopsy of the pulmonary lesion was performed.

The patients ranged in age from 6 to 73 years, the greatest number being between 40 and 60 (Table 1). Follow-up data are complete in 93 of the 96 cases. Many of these patients have been seen at regular intervals at the Clinic. In other instances, follow-up letters were answered by the patient, his relatives, or the home physician. In three cases it was not possible to obtain any information.

TABLE 1.—*Ages of Ninety-Six Patients Undergoing Pulmonary Resection for Metastatic Tumors*

Age, Yr.	Patients
0-9	3
10-19	2
20-29	10
30-39	16
40-49	26
50-59	26
60-69	12
70-79	1

The interval between treatment of the primary tumor and resection of the metastatic pulmonary lesion varied from zero to 22½ years (Table 2). As noted in the previous reports from the Clinic, the primary operation in all instances was curative in objective. In four patients the pulmonary operation was carried out prior to removal of the primary tumor. In two patients the primary lesions (squamous-cell carcinoma of the cervix) were treated by x-rays, following biopsy, and the uterus was not removed.

TABLE 2.—*Interval Between Treatment of Primary Tumor and Resection of Metastatic Pulmonary Tumors*

Interval from Primary Operation to Pulmonary Resection, Yr.	Patients
<1	26
1-2	20
2-3	14
3-4	16
4-5	7
>5	13

Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 20, 1958.

Fellow in Surgery, Mayo Foundation (Dr. Habein). Section of Surgery (Dr. Clagett) and Section of Surgical Pathology (Dr. McDonald), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Exclusive of the tumors of the three untraced patients, the lesions included 73 carcinomas, represented most frequently by tumors of the colon, rectum, and breast, but including such lesions as melanoma, teratoma of the testis, hypernephroma, and squamous-cell carcinoma of the cervix. One patient had two separate primary carcinomas of the breast. The remaining 20 primary lesions were classified as sarcomas, osteogenic sarcomas and fibrosarcomas being encountered most frequently. Both the primary and the secondary lesions in the tumor formerly reported by Hood and co-workers as being an osteogenic sarcoma are now considered to be malignant mesenchymomas. Similarly, the lesion listed as a giant-cell tumor in the earlier report has been reclassified as a chondrosarcoma.

As was found in the previous studies from the Clinic, the sex incidence was about equally divided, contrasting with the preponderance of males in primary bronchogenic carcinoma.

Clinical and Laboratory Aspects

The clinical and laboratory findings in these cases were variable. A total of 54 patients did not have any symptoms referable to the metastatic pulmonary tumor, the lesion having been found during routine thoracic roentgenography. The commonest symptom noted by the remaining patients was cough, which was present in 37; in 23 of these patients, the cough was productive, and gross hemoptysis was noted in 19. Five patients had thoracic pain as the chief complaint.

The roentgenologic findings in these patients have been well described by Hood and associates. All the patients had a roentgenologically discernible pulmonary lesion. Two lesions were present in each of eight patients, and three nodular densities were evident in the lung in one instance. Multiple lesions, when present, had the appearance of satellite nodules rather than that of widely disseminated metastatic masses.

The usual metastatic tumor in this group was characterized by a peripheral location, distinct margins, and homogeneous density. The diameter varied from 1 to 7 cm. Collapse of an upper lobe was present in one case, but obstruction of a significant amount of pulmonary tissue was not characteristic of these lesions. Calcification and cavitation were not observed in any of the tumors.

The great majority of these patients had no demonstrable pulmonary lesions at the time of operation on their primary tumors. In most instances, roentgenograms taken at that time had been recorded as normal, a finding that was upheld by later review. In only 10 instances was pulmonary metastasis known to have been present at the time of the primary operation. As mentioned previously, pulmonary resection was done prior to removal of the primary tumor in four of these cases.

Microscopic study of sputum or bronchial secretions or both for the detection of malignant cells was done in 35 patients. Atypical cells were found in 1 patient and definitely malignant cells in 13 others.

Bronchoscopy was done on 35 patients. Some abnormality related to the metastatic pulmonary process was found in 16 patients, and biopsy was productive of malignant tissue in 9.

Types of Pulmonary Resection

Lobectomy remains the commonest operation utilized at the Clinic in the surgical treatment of metastatic pulmonary tumors. Such a procedure was done on 60 patients. In 1 of these 60 patients, left lower lobectomy for metastatic melanoepithelioma was followed in two and a half years by metastasis in the right middle lobe. This second pulmonary lesion also was treated by lobectomy. Another of these patients had local excision of a second metastatic pulmonary growth, occurring after lobectomy on the same side. Twenty-four patients had pneumonectomy, and seven had segmental resection. Local or wedge excision of the metastatic tumor was carried out in five patients. In only two patients was it necessary to resect a portion of the thoracic wall or parietal pleura in treating the pulmonary tumors.

Survival After Pulmonary Resection

The risk of pulmonary resection in this group of patients was exceedingly low, only one death occurring in the immediate postoperative period; this took place one month after operation, while the patient was still in the hospital.

TABLE 3.—*Condition at Last Report of Ninety-three Traced Patients After Resection of Metastatic Pulmonary Tumors*

Survival Period After Pulmonary Resection, Yr.	Condition		
	Living Without Recurrence	Living With Recurrence	Dead
<1	6	2	25
1-2	1	3	19
2-3	3	3	9
3-4	5	1	2
4-5	3	1	0
5-6	2	0	0
6-7	3	1	1
7-8	2	0	0
8-9	0	0	0
9-10	1	0	0
Total *	26	11	56

* Excludes three untraced patients.

Table 3 indicates the condition of the 93 traced patients at the time of the last report or examination. Table 4 relates the survival periods to the types of primary tumor. A total of 56 patients have died, and another 11 patients, although living, have evidence of recurrent malignant tumors. Of the remaining 26 patients, 7 have been followed less than two years since resection of the metastatic lesion. This leaves 19 patients alive and apparently free of recurrent malignant disease two years or more after pulmonary resection.

Twenty-five patients died within one year and 19 others died within two years of the pulmonary operation. However, 12 patients, although finally dying of the malignant tumor, survived more than two years; and an additional 6 patients, despite recurrence, were living at last report, from two to six years after resection of the metastatic lesion. Thus, 37 of the 93 patients survived two or more years, and 22 survived three or more years, after resection of a metastatic tumor of the lung.

It is apparent from Table 4 that long-term survival was not limited to any particular group of tumors. Many early deaths occurred in patients with metastatic carcinoma from the colon, rectum, and breast, but a number of long survivals also were present in patients with these lesions after pulmonary resection. Although most of the patients with pulmonary metastasis from teratoma of the testis died soon after the thoracic operation, one patient at last report had survived seven years without evidence of recurrence. The patients with carcinoma metastasizing from the cervix did surpris-

TABLE 4.—*Length of Survival in Ninety-Three Patients at Last Report After Resection of Metastatic Pulmonary Tumors*

Primary Tumor	Cases	Length of Survival, Yr.					
		<1	1-2	2-3	3-4	4-5	>5
Carcinomas							
Colon, rectum	25	5	11	4	2	2	1
Breast	13	5	1	4		1	2
Melanoma	6	3	1	1	1		
Testis (teratoma)	6	4	1				1
Cervix (S. C. E.)	5	1			2	1	1
Kidney (hypernephroma)	4	2					2
Ovary	2	1					1
Cylindroma	3	1	1	1			
Uterus (adenocarcinoma)	2		1	1			
Parotid (mixed tumor)	1		1				
Jejunum (adenocarcinoma)	1	1					
Urinary bladder	1	1					
Larynx (S. C. E.)	1		1				
Extremity (S. C. E.)	1		1				
Thyroid	1				1		
Hemangioendothelioma	1			1			
Total	73						
Sarcomas							
Osteogenic	5	2	2		1		
Fibrosarcoma	6	3	2				1
Liposarcoma	2	1		1			
Ewing's	2	2					
Chondrosarcoma	1						1
Synovial	1	1					
Rhabdomyosarcoma	1			1			
Mesenchymoma	1				1		
Malignant hemangiopericytoma	1			1			
Totals	20	33	23	15	8	4	10

TABLE 5.—*Data on Sixteen Patients Living Without Evidence of Recurrence Three or More Years After Resection of Metastatic Pulmonary Tumors*

Age, Yr.	Sex	Primary Tumor and Site	Pulmonary Symptoms	Cytology	Bronchoscopy	Interval from Primary Operation to Pulmonary Operation, Mo.	Pulmonary Operation	Survival Since Pulmonary Operation, Mo.
52	M	Adenocarcinoma, rectum	Cough, sputum	Neg.	Neg.	66	Resection lingula, l. lung	55
49	F	Ca. sigmoid polyp	Cough, hemoptysis	Neg.	Neg.	60	Rt. lower lobectomy	80
61	F	Ca. rectum	Cough, sputum	Not done	Lesion rt. upper lobe bronchus	41	Rt. pneumonectomy	42
57	M	Ca. sigmoid	None	Neg.	Neg.	29	Rt. middle and lower lobectomy	41
62	F	Ca. sigmoid	None	N. D.	Not done	39	L. lower lobectomy	48
62	F	Ca. l. breast	None	N. D.	N. D.	15	L. lower lobectomy	49
39	F	Ca. rt. breast	Cough, sputum	Neg.	Neg.	120	L. lower lobectomy	94
49	F	Ca. l. breast	None	N. D.	N. D.	48	Resection lingula, l. lung	64
44	F	S. C. E. cervix	None	N. D.	N. D.	24	Rt. middle lobectomy	79
41	F	S. C. E. cervix	Cough, hemoptysis	Pos.	Neg.	48	L. pneumonectomy	42
51	F	Papillary ca. ovary	Cough, sputum	Neg.	Pos. biopsy	48	Rt. lower lobectomy	118
46	M	Hypernephroma	Cough, hemoptysis	Neg.	Tumor rt. main bronchus	48	Rt. pneumonectomy	75
26	M	Teratoma, testis	Cough	Pos.	Pos. biopsy	12	Rt. lower lobectomy	84
53	M	Adenoca. in thyroid adenoma	None	N. D.	Neg.	154	Rt. lower lobectomy	36
67	M	Chondrosarcoma l. leg	Cough, hemoptysis	N. D.	N. D.	18	Local excision lesion rt. upper lobe	71
25	F	Osteogenic sarcoma rt. leg	None	N. D.	N. D.	23	L. upper lobectomy	36

TABLE 6.—*Data on Eighteen Patients Who Died or Were Living with Recurrence Two or More Years After Resection of Metastatic Pulmonary Tumors*

Age, Yr.	Sex	Primary Tumor and Site	Pulmonary Symptoms	Cytology	Bronchoscopy	Interval from Primary Operation to Pulmonary Operation, Mo.	Pulmonary Operation	Interval from Pulmonary Operation to Recurrence or Death, Mo.
49	F	Ca. l. breast	None	Not done	Not done	10	Rt. lower lobectomy	26
50	F	Ca. both breasts *	None	N. D.	N. D.	21	L. pneumonectomy	29
53	F	Ca. l. breast	None	Pos.	N. D.	35	Segmental resection rt. middle & upper lobes	24 Pt. living
51	F	Ca. rt. breast	None	N. D.	N. D.	22	Rt. upper lobectomy	26
54	M	Ca. rectum	None	Neg.	Neg.	44	L. upper lobectomy	30
62	M	Ca. sigmoid †	None	Pos.	Neg.	0	L. pneumonectomy	24
41	M	Ca. sigmoid †	None	Neg.	Neg.	0	Rt. lower lobectomy	24 Pt. living
49	F	S. C. E. cervix	None	N. D.	N. D.	39	Rt. upper lobectomy	48 Pt. living
32	F	S. C. E. cervix	None	Pos.	N. D.	34	Rt. pneumonectomy	36
37	M	Melanoma l. leg	Cough, hemoptysis	Neg.	Lesion rt. upper lobe bronchus	40	Rt. pneumonectomy	25
64	M	Melanoma eyelid ‡	None	N. D.	N. D.	(1) 19	(1) L. lower lobectomy	36
						(2) 60	(2) Rt. middle lobectomy	Pt. living
42	F	Hypernephroma	Cough, hemoptysis	N. D.	Tumor l. main bronchus	37	L. pneumonectomy	66
20	F	Fibrosarcoma rt. leg ‡	Chest pain	N. D.	N. D.	(1) 132	(1) Rt. lower lobectomy	83
						(2) 169	(2) Local resection of lesion rt. lung	Pt. living
26	M	Hemangioendothelioma palate	None	Neg.	Lesion rt. upper lobe bronchus	120	Rt. pneumonectomy	31
53	F	Hemangiopericytoma l. thigh	None	N. D.	N. D.	0	Local excision	28
62	M	Mesenchymoma rt. scapula	Cough	Neg.	Tumor l. main bronchus	44	L. pneumonectomy	45
56	F	Adenoca. body of uterus	Hemoptysis	Neg.	Neg.	36	Rt. upper & middle lobectomy	27
50	F	Cylindroma submaxillary gland	None	N. D.	N. D.	84	Rt. lower lobectomy	32 Pt. living

* Patient had two separate primary breast carcinomas occurring almost two years apart; pulmonary operation 21 months after second radical mastectomy.

† Lesion in lung known to be present at time of operation on primary tumor.

‡ Had resection of two separate pulmonary metastatic tumors. Survival period is interval since first pulmonary resection.

ingly well as a group, with four of five surviving three or more years.

Study of our series disclosed little difference in prognosis between the patients who underwent pulmonary resection for metastatic carcinoma and those who had similar procedures for metastatic sarcoma. The patients with sarcomas and other tumors primary on the extremities in whom metastatic pulmonary tumors were treated by resection will be reported on in greater detail in another publication.[3]

In Table 5 are listed various data relative to 16 patients who were living at last report without evidence of recurrence three or more years after pulmonary resection for a metastatic tumor. Ten of these patients were included in previous reports from this institution. In this more favorable group, the age range was from 25 to 67 years. There were 6 men and 10 women. Five of the metastatic tumors originated in the colon or rectum, three in the breast, and two in the cervix; the other primary sites were ovary, kidney, testis, thyroid, and bone. It is apparent that the presence of symptoms does not exclude a favorable outcome after resection of a metastatic pulmonary tumor. Neither does the presence or absence of malignant cells in the sputum or positive bronchoscopic evidence of metastasis appear to influence the prognosis. In this small group of patients with relatively long survival, the extent of pulmonary resection varied from local excision of a metastatic lesion to pneumonectomy. Although considerable variation was present in the time interval from the primary operation to pulmonary resection (12 to 154 months), it is probably significant that late survival did not occur among patients who underwent resection of a pulmonary metastatic tumor within a year after the primary operation.

Table 6 contains data regarding 18 patients who died or were living at last report with recurrence of the malignant tumor two or more years after pulmonary resection of a metastatic growth. This group includes four patients with primary carcinoma of the breast and three patients with primary colonic or rectal carcinoma. It also includes two patients who have each undergone two separate pulmonary resections because of metastasis. One patient, a 64-year-old man, had a melanoma removed from an eyelid; 19 months later, left lower lobectomy was done for a solitary metastatic tumor; 41 months after this, or 5 years after the primary operation, a second metastatic growth was removed by right middle lobectomy. Similarly, a 20-year-old woman with fibrosarcoma underwent right lower lobectomy because of metastasis 11 years after excision of the primary tumor. After the pulmonary resection, it became evident that the primary lesion was not controlled, and another local excision was carried out at the primary site. Three years after the first pulmonary resection, two nodules of metastatic fibrosarcoma were removed by wedge excision from the right upper lobe; one month later, it was necessary to amputate the right leg for adequate control of the primary lesion. This patient was living, at last report, more than seven years after the second pulmonary resection for metastasis but showed recent evidence of recurrence in her sacrum and ilium.

Comment

Long-term survival after resection of a metastatic pulmonary tumor is well documented. Barney and Churchill,[4] in 1939, reported the first such case. Their patient survived 12 years after lobectomy for a metastatic tumor arising from a renal carcinoma, according to a follow-up report by Barney,[5] in 1944. Alexander and Haight,[6] in 1947, found only 5 published records of cases of this type, and they added 19 others from their own and other hospitals. Since that report, several reviews of the subject, in addition to the accumulated experience of various groups, have appeared in the literature.[1,2,7-11]

The appearance of a presumably solitary lesion in the lung at any time after the occurrence of a malignant tumor elsewhere in the body presents a difficult problem.

The possibility of the lesion being metastatic is great, but the remote chance that it represents a benign process or a second primary tumor is one of the reasons that exploratory thoracotomy should be considered seriously in this situation. The presence of an indeterminate pulmonary lesion in such a patient is perhaps often of even greater psychologic significance than it would be in the absence of a previous history of malignancy.

Furthermore, it has been well demonstrated in this and other series that the positive identification of a pulmonary metastatic tumor by either cytologic study of bronchial secretions or bronchoscopy does not always indicate an unresectable lesion or an eventually fatal situation.

The criteria for selection of patients for pulmonary resection for metastasis have been discussed by several authors.[1,2,6-11] Obviously, the patient must have a cardiorespiratory and general status that is sufficiently good to permit exploration and the necessary resection with little immediate risk. The primary lesion, as far as possible, should appear to be adequately controlled without evidence of local recurrence or other distant metastasis, such as to the skeleton or liver. Our study and the literature furnish some evidence that the duration of time from resection of the primary tumor to resection of the metastatic pulmonary growth is of prognostic significance. As already noted, we had no long-term survivors free of evident recurrence among patients in whom the metastatic pulmonary tumor developed less than a year after the primary operation.

Roentgenologically, the pulmonary lesion should be solitary, or, if multiple, the lesions should appear as satellite nodules rather than as a widespread process. In this regard, Lee [12] and Mandeville,[13] among others, have stressed the difficulty of establishing roentgenologically and with certainty the solitary nature of a pulmonary tumor.

It has been demonstrated repeatedly that considerable variation occurs in the biologic behavior of histologically similar tumors. Some of the patients in this series undoubtedly had malignant tumors characterized by little potential for growth, and this may account for the good results obtained in some situations. Unfortunately, no certain way exists at present of determining beforehand which patients will respond favorably after resection of a metastatic pulmonary tumor, and there will continue to be a good many disappointments in any such group of cases.

Radiation and drug therapy are usually of little value in metastatic tumors of the lungs, and yet something must be done for these patients. Surgical intervention is, at present, the only chance for cure and the best opportunity for palliation; although the possibilities of accomplishing these ends are often remote, we consider that exploration is definitely indicated in carefully selected patients.

Finally, before operation is undertaken, the patient, if he is an adult, should understand thoroughly the situation with regard to the possibilities in the event the pulmonary lesion is indeterminate in nature, and should be aware of the chances of ultimate cure if the lesion is malignant. Ample evidence exists that many of these difficult problems do not eventuate in hopeless situations.

Summary

A study has been made on 96 patients who had pulmonary resection for metastatic malignant lesions at the Mayo Clinic. Of the 93 traced patients, 16 were living without evidence of recurrence three or more years after the pulmonary operation. Although 44 patients died less than two years after the metastatic pulmonary lesion was removed, 12 patients lived two or more years before succumbing to the disease. Another six patients were alive despite recurrent malignant tumors two or more years after pulmonary resection. Although many of the results in this study were highly disappointing, some remarkable "cures" have been documented, and con-

siderable palliation has been afforded several patients.

The criteria utilized in the selection of these patients for surgical treatment are discussed. It is considered that resection is indicated for pulmonary metastasis in carefully selected cases. Other conditions being favorable, exploration should be considered seriously for an indeterminate pulmonary lesion in a patient with a previous history of malignancy.

Mayo Clinic.

REFERENCES

1. Seiler, H. H.; Clagett, O. T., and McDonald, J. R.: Pulmonary Resection for Metastatic Malignant Lesions, J. Thoracic Surg. 19:655-679 (May) 1950.

2. Hood, R. T., Jr.; McBurney, R. P., and Clagett, O. T.: Metastatic Malignant Lesions of Lungs Treated by Pulmonary Resection: Report of 43 Cases, J. Thoracic Surg. 30:81-89 (July) 1955.

3. Kroll, H. G.; Bickel, W. H., and Clagett, O. T.: Malignant Lesions of the Extremities with Solitary Metastasis to the Lungs: Unpublished data.

4. Barney, J. D., and Churchill, E. D.: Adenocarcinoma of Kidney with Metastasis to Lung Cured by Nephrectomy and Lobectomy, J. Urol. 42:269-276 (Sept.) 1939.

5. Barney, J. J. D.: Twelve-Year Cure Following Nephrectomy for Adenocarcinoma and Lobectomy for Solitary Metastasis, J. Urol. 52:406-407 (Nov.) 1944.

6. Alexander, J., and Haight, C.: Pulmonary Resection for Solitary Metastatic Sarcomas and Carcinomas, Surg. Gynec. & Obst. 85:129-146 (Aug.) 1947.

7. Effler, D. B., and Blades, B.: Surgical Treatment of Solitary Lung Metastasis, J. Thoracic Surg. 17:27-37 (Feb.) 1948.

8. Gliedman, M. L.; Horowitz, S., and Lewis, F. J.: Lung Resection for Metastatic Cancer: 29 Cases from the University of Minnesota and a Collected Review of 264 Cases, Surgery 42:521-532 (Sept.) 1957.

9. Groves, L. K., and Effler, D. B.: Surgery for Metastatic Neoplastic Disease in the Lung: Review of 38 Cases, Cleveland Clin. Quart. 23:16-27 (Jan.) 1956.

10. Kelly, C. R., and Langston, H. T.: Treatment of Metastatic Pulmonary Malignancy, J. Thoracic Surg. 31:298-315 (March) 1956.

11. Strieder, J. W.: Surgical Management of Neoplastic Pulmonary Metastases, New England J. Med. 254:1059-1062 (June 7) 1956.

12. Lee, I. N.: Pulmonary Metastases, Dis. Chest 30:85-95 (July) 1956.

13. Mandeville, F. B.: Roentgen and Clinical Problems in So-Called Solitary Metastatic Tumors in Chest, Am. J. Surg. 71:669-675 (May) 1946.

DISCUSSION

DR. JAMES BARRETT BROWN, St. Louis: May I ask a question? The opinion from Bethesda, if I am not mistaken, is that removal of the primary tumor may cause more metastases to show up. They may have been there, but they seem to show up when the primary tumor is removed. Is there any foundation clinically for that opinion in your experience, Dr. Clagett? This is in animals, of course.

DR. JOHN T. REYNOLDS, Chicago: In some cases the neurosurgeons are asked to operate on metastasis to the brain. I wonder if any of your patients who have had pulmonary metastases resected and also cerebral metastases which could be or needed to be resected?

DR. OSCAR T. CLAGETT, Rochester, Minn.: In reply to Dr. Brown's question, I don't believe that clinically I could agree with it. I am not very positive about it, but it has not been my own experience.

Replying to Dr. Reynolds' question, it has been done in a few instances. Tumors that metastasize to the lung can metastasize from the lung to the brain, and a few such patients have been operated on. I think something worthwhile has been accomplished, but not very often.

Treatment of Selected Adenocarcinomas by Perfusion Technique

KEITH REEMTSMA, M.D.; ROBERT F. RYAN, M.D.; EDWARD T. KREMENTZ, M.D., and OSCAR CREECH Jr., M.D., New Orleans

Two years ago the perfusion technique was introduced in the treatment of malignant melanomas of the extremity. The method involved perfusing a limb with a cancerocidal agent by means of an extracorporeal pump-oxygenator. This method allowed high concentrations of the drug to reach the involved extremity without the side-effects which accompany systemic administration of such agents. More recently this technique has been adapted to neoplasms of the lung, breast, pelvic organs, and rectum. A summary of the total experience with 75 cases appears elsewhere [1]; this report is concerned with 18 cases of adenocarcinoma.

Patient Material

Eighteen patients were included in this series. There were nine patients with carcinoma of the breast, four with carcinoma of the rectum, two with carcinoma of the ovary, two with metastatic carcinoma in an extremity, and one with endometrial carcinoma.

The patients with carcinoma of the breast selected for perfusion treatment fell into two groups. In the first group were those patients with extensive local disease satisfying the usual criteria of inoperability. The second group included patients with obvious axillary metastases when examined clinically but no evidence of inoperability. Both groups of patients were subjected to perfusion and simultaneous biopsy of lymph nodes at the apex of the axilla. Patients in the second group were subjected to radical mastectomy approximately three weeks after the perfusion treatment if the lymph nodes at the apex of the axilla were negative. In the first group of patients the perfusion treatment was considered palliative, and in the second group it was considered adjuvant therapy.

TABLE 1.—*Cases of Adenocarcinoma Treated by Perfusion*

Breast carcinoma	9
Rectal carcinoma	4
Ovarian carcinoma	2
Metastatic adenocarcinoma to an extremity	2
Endometrial carcinoma	1
Total	18

Of the four patients with adenocarcinoma of the rectum, three previously had undergone abdominoperineal resections. Each showed evidence of locally recurrent disease without widespread metastases. One patient had inoperable rectal carcinoma when first seen. The two patients with ovarian carcinoma both had previously undergone laparotomy and oophorectomy, and both showed evidence of local pelvic recurrences. The patient with endometrial carcinoma showed evidence of locally recurrent disease in the pelvis and ilium, which had not responded to x-ray treatment or systemic administration of cancerocidal drugs. Two patients in this series had local metastases in an extremity—in one secondary to a renal neoplasm treated five years previously by nephrectomy; in the other diagnosed as metastatic adenocarcinoma of the extremity, primary site undetermined.

Methods

The technique of the perfusion method involved cannulation of the artery and vein supplying and draining the involved areas, with exclusion of the

Clinical Fellow, American Cancer Society (Dr. Ryan).

Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 20, 1959.

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TABLE 2.—*Perfusion for Breast Carcinoma*

Case No.	Agent	Decrease in Size of Tumor	Microscopic Evidence of Regression	Result	Follow-Up Period, Mo.
1	HN_2*	Yes	Probable	Controlled	8
2	HN_2	Undetermined	No	Controlled	6
3	HN_2	Undetermined	Probable	Controlled	6
4	HN_2	No	Not evaluated	Patient lost to follow-up	
5	HN_2	No	Probable	Controlled	6
6	HN_2	Probable	Probable	Died	
7	Actinomycin D	Yes	No	Recurrent	5
8	Actinomycin D	Yes	Not evaluated	Controlled	3
9	TSPA	Not evaluated	Not evaluated	Too recent for evaluation	1

* HN_2 indicates mechlorethamine.

remainder of the body. For lower-extremity lesions either the iliac or the femoral artery and vein were cannulated, and a tourniquet was placed proximal to the cannulae. The cannulae were then connected to the extracorporeal pump-oxygenator, and the cancerocidal agents were introduced into the perfusate.

The technique for perfusion for locally recurrent pelvic and rectal disease has undergone several modifications. In the early cases catheters were inserted into the aorta and vena cava distal to the renal vessels. Pneumatic tourniquets were placed around the upper thighs and were inflated at the time perfusion was begun. The first modification of this technique involved inserting the catheters through the femoral artery and vein into the terminal aorta and vena cava, which were then occluded above the tips of the catheters. The most recent modification, still under development, involves the use of balloon-tipped catheters introduced into the femoral vessels and passed into the terminal aorta and vena cava, with occlusion of these vessels by inflated balloons. The last method avoids the necessity of laparotomy.

The technique for perfusion of breast lesions involved cannulation of the subclavian artery and vein at the apex of the axilla, with inflation of a previously placed pneumatic tourniquet about the upper arm. Recently the use of retrograde cannulation with balloon-tipped catheters from the brachial vessels to the subclavian artery has been under investigation.

The cancerocidal agents used in this series of patients included mechlorethamine (nitrogen mustard), triethylene thiophosphoramide (TSPA) and actinomycin D. The drugs used in the patients with breast cancer are itemized in Table 2. Mechlorethamine was used in all cases of rectal carcinoma and in the patient with endometrial carcinoma. TSPA was used in the two patients with ovarian carcinoma, and actinomycin D was used in the two patients with metastatic adenocarcinoma of the extremity. The drug dosage was as follows: mechlorethamine, 0.4-0.8 mg/kg.; TSPA 0.8-0.9 mg/kg.; actinomycin D 50μg.-55μg. per kilogram.*

Results

In the evaluation of results, patients have been placed in the following categories: (1) dead; (2) disease controlled (no evidence of persistent disease); (3) disease quiescent (known residual malignant disease which appears inactive); (4) recurrent (persisting or recurrent active malignant disease).

There was one death in this group of 18 patients. This occurred three weeks after perfusion for breast carcinoma in a 70-year-old patient whose postoperative course had been uneventful until a few minutes before death. At that time she complained of sudden chest pain and showed severe dyspnea and cyanosis. She collapsed and died within a period of several minutes, and the clinical diagnosis was myocardial infarction or pulmonary embolus. Permission for autopsy was not obtained.

The remaining 17 patients are alive, for periods of 1 to 14 months since operation. The four cases of rectal carcinoma must be classified as recurrent disease, and the perfusion appeared to have no effect on their clinical courses. Among the eight living

* The drugs were supplied by the following men: mechlorethamine, by James M. Sherwood, Merck Sharp & Dohme, Division of Merck & Co., Inc.; actinomycin D, James M. Ruegsegger, M.D., Lederle Laboratories Division, American Cyanamid Company.

patients subjected to breast perfusion, the disease in one is classified as quiescent, in one as recurrent, and in five as controlled. In one the perfusion has been done too recently for evaluation. One case, originally classified as inoperable on the basis of large, fixed axillary nodes, showed regression of the tumor and the axillary mass following perfusion, and the patient was subsequently subjected to radical mastectomy. The case of endometrial carcinoma is classified as controlled, and one case of ovarian carcinoma is classified as quiescent. The remaining patients have been treated too recently to permit evaluation of results.

The complications in these patients may be divided into two groups: (1) complications related to bone-marrow depression by the cancerocidal agents, and (2) complications from the surgical procedure itself.

In the first group, only one patient showed depression of the white blood cell count depression below 2,000 per cubic millimeter. Of the nine cases of breast carcinoma perfused, none showed a depression of the white cell count below 4,000. In patients subjected to perfusion for pelvic or rectal lesions the depression of the white cell count was usually somewhat more pronounced, although no complications attributable to bone-marrow depression appeared in any of the patients in this group.

Complications attributable to the surgical procedure included two cases of axillary-vein thrombosis observed at the time of radical mastectomy following perfusion. One of these patients showed swelling of the arm, which subsided with the usual methods of treatment.

Comment

The effectiveness of the perfusion technique has been demonstrated in the treatment of melanomas of the extremity.[2] The role of the method in the treatment of lesions of the pelvis and breast is more difficult to assess.

The evaluation of results in breast cancer is particularly difficult. The natural history of these lesions is frequently long, and any claims based on a short period of observation must be guarded. Another factor is that the microscopic appearance of breast cancer may be quite variable in different areas of the same tumor, and areas of necrosis are occasionally seen in untreated lesions. For this reason the evaluation of the effects of treatment based on microscopic appearance of the lesion may be misleading. In this series a probable effect on the microscopic appearance of the tumor and a decrease in size of the gross lesion were observed in four of six cases in which such factors were evaluated. In one of these cases, previously classified as inoperable, regression of the primary tumor and fixed axillary nodes permitted subsequent radical mastectomy.

The results in four cases of recurrent rectal carcinoma were discouraging. In no case was there observable regression of tumor. The case of endometrial carcinoma treated by perfusion has been published in detail previously,[3] and the patient showed evidence of gross and microscopic regression of tumor. Of the cases of ovarian carcinoma, one is too recent to evaluate, while the other showed regression of tumor and is now classified as quiescent. The two patients with metastatic carcinoma in the extremity have been perfused too recently for evaluation.

The present study demonstrates that regional perfusion for pelvic and breast lesions is a feasible procedure. The maintenance of constant flow rates for periods up to one hour and the infrequency of bone-marrow depression suggest that some degree of isolation of the involved areas is obtained. Perhaps with other cancerocidal drugs or combinations of such agents, a more marked response may be obtained in adenocarcinomas.

Summary

Eighteen patients with adenocarcinoma have been treated by the perfusion technique. The method involved cannulation of the artery and vein supplying the involved

area and perfusion with canceroidal drugs by means of a pump-oxygenator.

Nine patients with breast carcinoma, four with unresectable rectal carcinoma, two with ovarian carcinoma, two with metastatic adenocarcinoma to the extremity, and one with endometrial carcinoma are included in this series.

The follow-up period is too short to allow complete evaluation. The majority of breast carcinoma patients in whom tumor response could be evaluated showed some evidence of gross and/or microscopic regression. Responses of the other tumors were variable.

Department of Surgery, Tulane University School of Medicine.

REFERENCES

1. Creech, O., Jr.: Experiences with Isolation-Perfusion Technic in the Treatment of Cancer, Ann. Surg., to be published.

2. Creech, O., Jr.; Ryan, R. F., and Krementz, E. T.: Treatment of Melanoma by Isolation-Perfusion Technic, J. A. M. A. 169:339-343 (Jan. 24) 1959.

3. Creech, O., Jr.; Krementz, E. T.; Ryan, R. F., and Winblad, J. N.: Chemotherapy of Cancer: Regional Perfusion Utilizing an Extracorporeal Circuit, Ann. Surg. 148:616-632 (Oct.) 1958.

4. Ryan, R. F; Krementz, E. T.; Creech, O., Jr.; Winblad, J. N.; Chamblee, W., and Cheek, H.: Selected Perfusion of Isolated Viscera with Chemotherapeutic Agents Using an Extracorporeal Circuit, S. Forum 8:158-161, 1958.

DISCUSSION

DR. JOHN S. STEHLIN JR., Houston, Texas: Dr. Creech and his group are to be congratulated upon their fine work. We learned the basic technique of perfusion from them last year and began employing the procedure at the M. D. Anderson Hospital and Tumor Institute in December, 1957. Thus far, we have performed 56 perfusions. The majority have been for melanoma, involving chiefly the extremities. As a group, these lesions have shown the most impressive changes, both clinically and histologically.

The two major limiting factors in determining the maximum dosage of the chemotherapeutic agent are (1) the local tissue tolerance, i. e., the amount of drug which the normal tissues can tolerate without being permanently damaged, and (2) the amount of the drug which leaks into the systemic circulation. With respect to the local tissue tolerance, we know from experience the maximum dose of nitrogen mustard or phenylalanine mustard which can be perfused into the extremities without causing blistering or gangrene. From studies utilizing radioactive iodinated serum albumin, commonly known as RISA, we also are able to predict the amount of leakage. When perfusions of the extremities are done distally, as at the popliteal level, leakage is practically nil. As one approaches the trunk, however, it increases. Perfusion at the femoral or iliac level is associated with leakage of approximately 20% of the drug, even though the tourniquet is tightly applied and the extremity washed out with dextran and whole blood at the conclusion of the procedure. In aortic perfusion, for which tourniquets are applied to both thighs and one arm, and the aorta, vena cava, inferior mesenteric vein, splenic pedicle, and epigastric vessels are clamped, the percentage of mixing or leakage is extremely high at the end of one hour. The one limiting factor in determining the maximum dose of the chemotherapeutic drug at the popliteal level is therefore the local tissue tolerance, whereas at more proximal levels, i. e., the femoral, iliac, axillary, subclavian, or aortic, both local tissue tolerance and leakage are important considerations.

We believe that perfusion offers interesting possibilities in the treatment of patients with malignant disease. The procedure possesses several possible advantages as an adjuvant to surgery. First, it is conceivable that solid tumors may be destroyed by regional perfusion, although at present the prospects of success in this respect appear remote. Perfusion may damage malignant cells within a solid tumor, however, and thus reduce the likelihood of subsequent difficulty incident to dissemination or implantation during conventional surgical excision. Second, more conservative excisions or amputations, especially for tumors of the extremities, may be possible following regional perfusion. Third, it is also possible that certain tumors which are technically inoperable, such as those in the pelvis, may be rendered operable by this method. Fourth, perfusion may be advantageous in reducing the incidence of latent metastases by destroying loose tumor cells within regional lymphatics, or perhaps vascular channels.

Finally, prophylactic perfusion of isolated organs commonly the sites of metastases may be feasible.

Whether perfusion will become an accepted procedure in the care of patients with malignant disease remains to be seen. At present, we do not recommend the operation as a standard therapeutic weapon, since thus far we have only impressions as to its efficacy. Additional time and study will be necessary for an accurate evaluation.

DR. HARRY W. SOUTHWICK, Chicago: I think the essayists are to be congratulated on their rather ingenious method of introducing a fairly large quantity of chemotherapeutic agent into a relatively isolated area without significant risk to the systematic circulation. I should like to echo Dr. Stehlin's comments, however, insofar as the relative isolation is concerned. Recently, in perfusing a patient who had a recurrent carcinoma of the colon with the pelvis fixed, we found, using RISA, that almost 35% of the tagged material leaked through into the peripheral circulation in 20 minutes. Of course, perfusing the aorta below the region of the adrenals is bound to allow for leaks both through the lumbar and through the portal system. However, we have also found in 22% leak in 20 minutes in perfusing an "isolated" extremity via the femoral vessels many months after a radical groin dissection; utilizing a fairly short-acting drug, however, such as mechlorethamine, the systematic difficulties which may be encountered associated with this leak are not significant as far as we can tell by our present tests. With other, long-acting drugs, such as procaine penicillin G U. S. P. (PAM), the complications may be of disastrous proportions.

[Slide] Through the cooperation of Dr. Leroy Long Jr. and his associates, we made some smears from the blood at the vena-cava side of our pump system. I think you will see without difficulty the normal white cells in the area and then the rather large tumor cell which is present here. [Slide] In this slide is seen a similar markedly enlarged, atypical cell which was found in the venous circuit just prior to perfusion. It is interesting to note (and I make no comment as far as the over-all therapeutic effectiveness is concerned) that these cells disappear completely from the venous circuit after the injection of mechlorethamine into the isolated area in four divided doses five minutes apart, each calculated on the basis of 1.5 mg. per kilogram of total body weight.

DR. JOHN T. REYNOLDS, Chicago: Concerning the question Dr. Reemtsma mentioned—the use of the catheter introduced up through the arteries—I should like to mention that Dr. Guynn and I recently had a patient who was sent to us for closure of a colostomy after having had irradiation for carcinoma of the cervix. Both the gynecologist and the internist who saw this patient at the time felt that she had a far-advanced and utterly inoperable carcinoma, and that any surgical intervention was unnecessary. Actually, at laparotomy the vaginal finding was completely disproved. The patient had no carcinoma at all. The distortion felt at vaginal examination was not carcinoma, but was tense cardinal ligaments rendered fibrotic by the irradiation effect. If the laparotomy had not been done, she would have been thought to have a far-advanced carcinoma. This finding emphasizes again that curative irradiation should not be carried out without a microscopic confirmation of the nature of the lesion under treatment.

DR. WILLIAM H. SNYDER JR., Los Angeles: We had a 4-week-old baby with sarcoma of the thigh who had been given extensive x-ray therapy because there was evidence of metastasis higher up. He was also given mechloramide and tetracycline B, without effect. The lesion was increasing in size, becoming more fungating, with breaking down of the tissue. We talked with Dr. Creech, and he suggested we go ahead with the technique we had heard him describe in an original paper some time before. As a result of this treatment, the lesion disappeared practically entirely. So it appeared as though we had a miraculous result, or at least something that none of the other modes of therapy had produced. However, within three months it recurred. At least the method offers a means of controlling an ulcerating sarcomatous lesion that no other could control.

DR. KEITH REEMTSMA, New Orleans: In regard to Dr. Stehlin's and Dr. Southwick's comments regarding leakage, we agree that there is considerable spill-over during aortic and pelvic perfusion. We use only the short-acting agents and have avoided phenylalanine mustard in such cases. Regarding Dr. Reynolds' comment, we insist on microscopic confirmation in these patients prior to perfusion.

I was interested in hearing Dr. Snyder's report. We had a similar case of rhabdomyosarcoma which disappeared after perfusion, only to recur in about three months.

Effect of Triethylenethiophosphoramide (Thio-TEPA) upon Healing of Abdominal Wounds

S. M. FARHAT, M.D.; D. M. MILLER, M.D., and M. M. MUSSELMAN, M.D., Omaha

Triethylenethiophosphoramide (thio-TEPA) and mechlorethamine (nitrogen mustard) are used at the time of operation for cancer to discourage the local and distant implantation of the cancer cells in the body. If these cytotoxic drugs are capable of destroying the malignant cells, it is logical to question whether they might also affect the young and proliferating cells of a healing wound. In a previous report [1] we showed experimentally that mechlorethamine interfered with the healing of wounds and reduced their tensile strength. Mechlorethamine also caused weight loss in animals (Fig. 1). We were, however, unable to determine whether reduction of tensile strength was a direct result of mechlorethamine on the healing wound or secondary to malnutrition (as manifested by loss of weight).

In the present study we have determined the effect of thio-TEPA on the healing of abdominal wounds in rats. The results suggest that thio-TEPA, in contrast with mechlorethamine, does not reduce the tensile strength of the wound and does not cause significant malnutrition in animals.

From the Department of Surgery, University of Nebraska College of Medicine.

Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 20, 1958.

Lederle Laboratories Division, American Cyanamid Company, provided the triethylenethiophosphoramide used in this experiment as thio-TEPA.

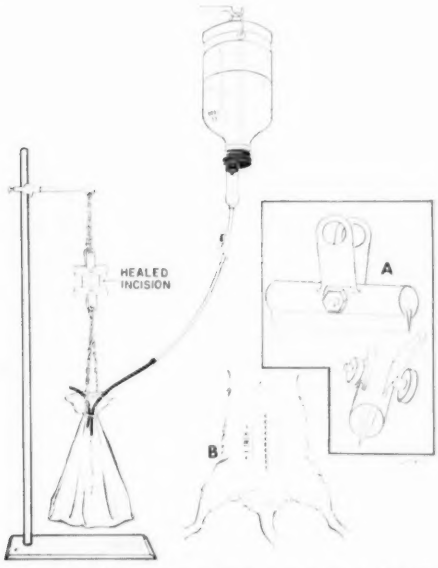

Fig. 1.—Distribution of rats in relation to the tensile strength of their wounds.

Material and Methods

Rats of mixed sex, weighing from 150 to 235 gm., were selected. Under ether anesthesia, the abdomen was shaved, and, with aseptic technique, an incision was made in the midline through all layers of the abdominal wall. The incision then was closed with running through-and-through 00000 silk sutures. Two groups of animals were studied. In Group 1, 37 rats were given a single dose of 0.6 mg. of thio-TEPA per kilogram of body weight just before closure of the incision. In Group 2, 30 rats, serving as controls, were operated upon in a similar fashion, but, instead of thio-TEPA, isotonic saline was injected into the vena cava. Food and fluid were allowed ad lib to both groups.

All animals were killed after seven days, and a segment of the abdominal wall containing 1 in. of the incision was excised. The sutures were removed, and the tissue was placed between two clamps, as shown in Figure 2. Water was run at a constant rate into the plastic bag attached to the lower clamp. The weight of water causing disruption of the wound was taken as the tensile strength of the wound.

Animals were killed after seven days to permit passage of the normal lag period of healing. Rapid wound healing takes place from the fourth to the seventh day, as shown by Carrel [2] and Howes.[3]

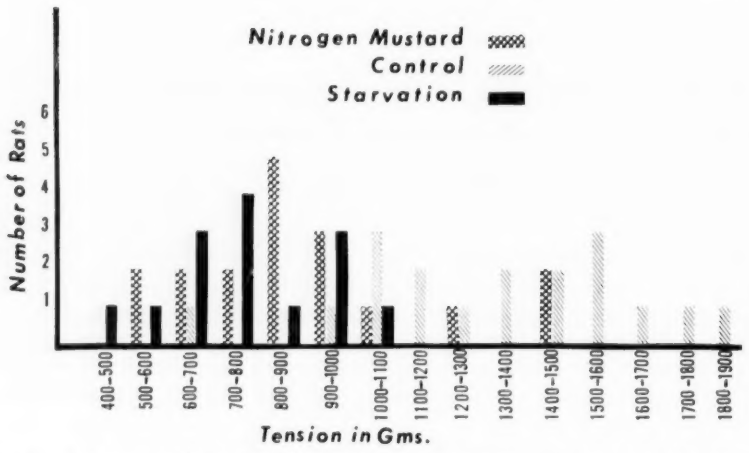

Fig. 2.—Apparatus used for determination of tensile strength. The weight of the water in the plastic bag that caused wound disruption was taken as the tensile strength of the wound.

Sections of the wound margins were obtained for histologic studies.

Results

The results are shown in the accompanying Table. The average weight loss after operation in animals receiving thio-TEPA was 3.6 gm. In these animals the tensile strength of the wound ranged from 600 to 1,700 gm. The average strength was 970 gm. (median, 900 gm.). In the control group (the average weight loss was 1.5 gm.; the tensile strength of the wound ranged from 600 to 1,850 gm., and the average strength was 1,090 gm. (median, 1,025 gm.).

The sections of wound margins were stained by Wilder's stain for reticulum and by Masson's stain for collagen. There was no significant difference between the two groups in either the characteristics or the amount of collagen and reticulum. Foreign-body reaction and infection were more marked in the group receiving saline than in that receiving thio-TEPA. The wounds of some of the animals receiving thio-TEPA were infected with actinomycetes, and characteristic sulfur granules were noted. We have no explanation for this observation.

Average Weight Loss in Animals Receiving Thio-TEPA *

Group	No.	Weight Change, Gm.	Tensile Strength, Gm.
Thio-TEPA (0.6 mg/kg.)	37	−3.6	970
Control	30	−1.5	1,090

* The average weight loss was about the same in animals receiving thio-TEPA as in the controls. The average tensile strength was not significantly reduced in the group receiving thio-TEPA.

Comment

Triethylenethiophosphoramide (thio-TEPA) is a polyfunctioning, alkylating agent, belonging to the group of compounds that contain ethyleneimine rings. This cytotoxic drug is being used more and more in the chemotherapy of cancer. Shay [4] and others used this drug in experimental animals with leukemia and sarcoma. Later its use was extended to the treatment of cancer of the breast and ovary, malignant melanoma, and others. Recently thio-TEPA has been used at the time of operation, or immediately after operation, to discourage the chance of implantation of the free-floating cancer cells.

The cytotoxic action of thio-TEPA is attributed to changes produced in the chromosomes by reaction with nucleic acids, stopping mitotic division in its early phase.

This action is preferentially, if not exclusively, directed toward multiplying cells of all types.

In our previous experiments we noted that mechlorethamine caused a statistically significant reduction in tensile strength of the wounds, as well as considerable loss of weight in rats. This raised the question whether thio-TEPA would have a similar effect on wound healing. We found that thio-TEPA did not reduce the tensile strength of 7-day-old wounds or interfere with nutrition in rats.

Summary and Conclusions

Triethylenethiophosphoramide (thio-TEPA) has been used experimentally and clinically as a cancerocidal agent in the treatment of various neoplasms. This drug arrests the mitosis of young and proliferating cells. In this study we found that thio-TEPA did not interfere with healing of abdominal wounds in rats. We could demonstrate no interference with or alteration in the fibroblastic proliferation or collagen deposition.

From these findings we conclude that the administration of thio-TEPA has no effect on the rate of wound healing and does not reduce the tensile strength of wounds.

University of Nebraska College of Medicine (Dr. Musselman).

REFERENCES

1. Farhat, S. M.; Amer, N. S.; Weeks, D. S., and Musselman, M. M.: Effect of Mechlorethamine Hydrochloride (Nitrogen Mustard) on Healing of Abdominal Wounds, A. M. A. Arch. Surg. 76:749, 1958.

2. Carrel, A.: The Treatment of Wounds, J. A. M. A. 55:2148, 1910.

3. Howes, E. L.; Sooy, J. W., and Harvey, S. C.: Healing of Wounds as Determined by Their Tensile Strength, J. A. M. A. 92:42, 1929.

4. Shay, H., and others: Treatment of Leukemia with Triethylene Thiophosphoramide (Thio-TEPA): Preliminary Results in Experimental and Clinical Leukemia, A. M. A. Arch. Int. Med. 92: 628, 1953.

DISCUSSION

DR. R. C. HARRISON, Edmonton, Alta., Canada: I have enjoyed this paper very much, and must make a comment on it. Dr. W. C. MacKenzie, Dr. F. Gouws, and Dr. W. Pisesky, in our laboratory, have studied this problem, and their results would indicate that both mechlorethamine and thio-TEPA retard wound healing in rats. This undesirable effect on wound healing can be prevented by the simultaneous administration of norethrandrolone (Nilevar).

Adrenal-Corticoid Depression of Adrenal Estrogens in Cases of Mammary Cancer

GEORGE E. BLOCK, M.D., M.S. (Surg.); JACK D. McCARTHY, M.D., and A. BURGESS VIAL, M.D., Ann Arbor, Mich.

Introduction

The demonstration by Beatson in 1896 that castration would effect remissions in advanced breast cancer heralded the advent of ablative therapy in this disease.[1] In 1951 Huggins obtained clinical remissions following bilateral adrenalectomy in the absence of ovarian function.[2] Huggins' work was not a chance clinical discovery, but was a logical result of prolonged experimentation and observation of the role of the steroid hormones in neoplasia.[3] At the time of Huggins' first adrenalectomy, he postulated that the method of palliation was through the elimination of endogenous estrogen production by the host.[4] Since that time, the estrogen-elimination theory of postadrenalectomy remissions has been questioned,[5] but no more attractive explanation has been advanced.

The welcome remissions associated with adrenalectomy have encouraged some surgeons to remove empirically the adrenals of patients with far-advanced breast cancer.[6] However, since over half the patients subjected to adrenalectomy receive no benefit and are subject to the unpleasant metabolic effects of adrenal removal in the face of advancing disease, the operation has been abandoned as a routine procedure by some clinics.[7]

The depression of adrenal function by the administration of corticoids has been accomplished in instances of adrenal hyperplasia,[8] and the treatment of collagen diseases with adrenal steroids has resulted in adrenal insufficiency.[9] It was, therefore, a logical step to attempt pharmacological depression of adrenal function in mammary cancer patients in the hope of obtaining remissions without the necessity of a major operative procedure, with its associated morbidity and mortality. Lemon[10] has reported remissions in a well-controlled series of patients using cortisone and popularized the concept of "medical adrenalectomy." Pearson[11] found that corticoid depression of the adrenals gave profound clinical remissions in 30% to 50% of his cases. Other workers, using only objective criteria, have reported definite remissions in a few patients, but realize that the remission rate is appreciably lower than that associated with adrenalectomy.[12]

We have undertaken to study the effect of adrenal-cortical administration in order to determine the efficacy and mode of action of these substances in achieving palliation from advanced breast cancer.

Material

In this study to date, seven female patients suffering from far-advanced mammary cancer have been studied. Two of the patients were lost to follow-up, so that this preliminary report deals with only five. It should be noted that we have treated several patients with corticoids, but as yet only seven have been subjected to the conditions of the study. All patients were white women. The youngest was 27 years of age and the oldest 74. The average age of the patients studied was 50.2 years.

Method

The patients included in this study were all castrated women suffering from far-advanced mammary cancer. The extent of the disease was established and base-line determinations were made of

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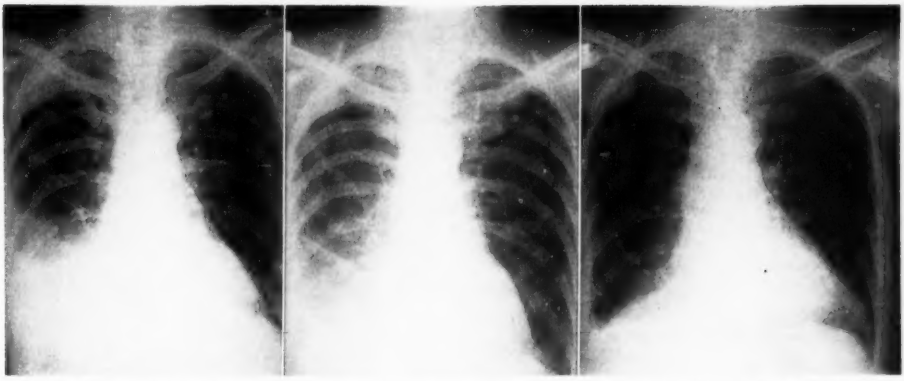

Fig. 1.—Pre- and post-treatment roentgenograms showing decrease in pleural fluid without thoracentesis. Remission, of 13 months' duration, continues at time of this report.

the urinary estrogen excretion over a 24-hour period. These determinations were made by methods of bioassay and paper chromatography. The bioassay method is essentially that of Smith and Smith,[18] while the chromatographic method is a modification of the technique described by Zaffaroni[14] and Bloch.[15] After these determinations, the patients were administered hydrocortisone orally in the amounts of 100-150 mg. per day for at least 30 days. At the end of the 30-day period, estrogen excretions were again determined. This determination was repeated at monthly intervals. Subsequent to one month of treatment with hydrocortisone, and at monthly intervals thereafter, the response of the patient's disease process was evaluated, and remissions, if any, were judged by generally accepted objective criteria.[7]

Results

Clinical Results.—Four of the five patients studied underwent objective remissions while receiving hydrocortisone. One patient who suffered from pulmonary metastases with pleural effusion was markedly benefited and has been asymptomatic for 13 months. This patient had consistently demonstrated malignant cells in the pleural effusion (Fig. 1). In addition to the pulmonary metastases, the patient also had a cutaneous lesion at the midsternal region. This lesion acted as a barometer for the efficacy of the steroid treatment in that at levels of 100-150 mg. of hydrocortisone per day, the lesions would shrink and become painless. When the dose of hydrocortisone was decreased to 70 mg. per day, the lesion increased in size and became painful. Again, with increasing doses of hydrocortisone, the lesion regressed.

Remissions were seen without relation to the site of the metastatic disease. Three of the patients had primarily soft-tissue metastases; one had skeletal lesions, and one suffered from pulmonary involvement. The one patient of the series who did not benefit from hydrocortisone therapy had massive hepatic involvement. The youngest patient in this small series received no benefit, while the oldest patient had both objective and subjective improvement.

Remissions ranged from 3 to over 13 months in duration. One remission was for nine months, followed by exacerbation of the disease. The other three patients had remissions of 3, 9, and 13 months, respectively, and are still experiencing remissions.

All of the patients who received hydrocortisone in excess of 100 mg. per day gave evidence of subjective improvement, as demonstrated by renewed vigor, increased appetite, or a general sense of well-being.

Estrogen Excretion.—Estrogen excretions fell markedly from pretreatment levels in the four patients who had remissions with hydrocortisone therapy (Table). In two patients, total estrogen excretion fell from over 2μg. per day to below the level of sensitivity by bioassay (1μg. to 2μg.). In the other two patients whose estrogen excretion was measured by chromatography

Estrogen Excretions Before and After Treatment with Hydrocortisone in Castrate Female Patients *

Patient	Age	Status	Pretreatment Excretion, μg.				Post-Treatment Excretion, μg.			
			Total	Estrone	Estradiol	Estriol	Total	Estrone	Estradiol	Estriol
Successful (remission)										
1	74	Castrate	2				<2			
2	60	Castrate	2.5				<2			
3	49	Castrate	1.68	1.68	0	0	0.24	0	0	0.24
4	41	Castrate	3.89	1.57	0	2.32	0.48	0	0.48	0
Failure (no remissions)										
5	27	Castrate	<2				<2			

* Note total estrogen excretions as well as fractions.

before and after treatment, a fall in total estrogen, as well as a marked depression in the estrone and estriol fractions, was observed.

The one patient who did not receive benefit from hydrocortisone administration had such a low level of estrogen excretion prior to treatment that by bioassay methods the excretion was less than the level of sensitivity and by chromatographic means the excretion was less than 1μg. per day.

Comment

That four or five patients studied experienced remissions with hydrocortisone administration is an unexpectedly high percentage of success, and it is our opinion that this result is merely fortuitous. In a larger series (over 20 patients) of our cases treated with hydrocortisone who did not have pre- and post-treatment determinations of estrogen excretion, (and, therefore, were not eligible to be included in this study), the remission rate was a great deal lower—perhaps 1 in each 10 patients treated.

Admittedly, this series is a small one, and must be expanded greatly for the results to be fully understood. However, the uniform decrease in estrogen excretion in the four patients undergoing remission in worthy of note. Patient 3 (Table) had a significant depression of the estrone fraction of the total estrogens following treatment. Both the estrone and the estriol fraction were depressed in Patient 4 after treatment. Estrone and estriol are primarily adrenal in origin, although small amounts may be produced elsewhere.[16] From these observations, in the face of absence of ovarian function, one can presume that following hydrocortisone administration there is a decrease in the adrenal production of estrogens and that this, in turn, is the mechanism of remissions obtained from hormone-sensitive breast tumors. This would support Huggins' initial concepts of steroid hormone ablation.[4]

An understanding of the basic physiologic mechanisms whereby corticoid administration brings about a decrease in adrenal estrogen has been elucidated by Lemon and his co-workers.[10,17] Lemon has demonstrated that the adrenal production of estrogen is mediated through the pituitary by the action of the adrenocorticotropic hormone (corticotropin). Lemon feels that exogenous corticoids act as a blocking agent of pituitary corticotropin, decreasing adrenal-estrogen (and corticoid) production. In association with this phenomenon, it is pointed out that the administration of corticoids to patients whose ovaries are intact is not without danger. The possibility exists that the adrenal-estrogen production acts in an inhibitory capacity to the elaboration of pituitary gonadotropin (FSH). A depression of the adrenal-estrogen production by corticoids may well cause an increase in pituitary gonadotropic production by the elimination of the FSH-blocking effect of the adrenal estrogens and incite renewed estrogen production in a previously dor-

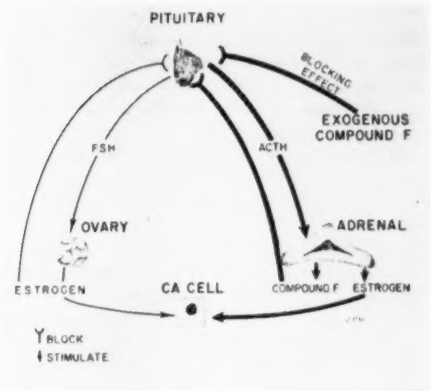

Fig. 2.—Pituitary-adrenal-gonadal axis. A schematic representation of the pituitary tropic hormones and the pituitary-blocking effects of gonadal and adrenal estrogens, as well as the pituitary-blocking effect of exogenous hydrocortisone (Compound F).

mant ovary (Fig. 2). Cortisone itself has not been shown to be converted to estrogens, but high doses of cortisone have been associated with increased 17-ketosteroid production, suggesting androgenic transformation.[18,19]

To eliminate the variable of ovarian-estrogen production either before or after administration of hydrocortisone, the patients in this series were restricted to those who had been previously castrated. Therefore, any change in the estrogen excretion can be interpreted as being from depression of the intact adrenals. The degree of adrenal depression cannot be absolutely ascertained by the methods employed by us, as minute amounts of estrogen measured in the urine may represent larger amounts and more physiologically active steroids present as circulating hormones. Nevertheless, a trend is shown, and this trend corresponds to the concept of adrenal depression by corticoids and the resultant decrease in adrenal-estrogen production. The associated objective remissions in the face of decreased adrenal-estrogen production lead us to believe that these remissions were the result of corticoid administration, causing a decreased adrenal-estrogen output and the resultant change in the internal endocrine environment of the host.

The frequently observed subjective improvement in patients receiving steroid therapy should not be mistaken for actual regression of the tumor. In this series only objective remissions were judged. It is, however, of value to be able to employ the corticoid-induced euphoria in the terminally ill patient. One patient in our series became euphoric. Also, patients may receive benefit from corticoid administration by relief of hypercalcemia and abrogation of symptoms associated with metastases to the central nervous system and liver, where the derangements are primarily those of obstruction induced by local inflammation. The well-known properties of the adrenal corticoids in reducing inflammatory response are assumed to be the mechanism of action in these situations.[20]

Protein catabolic effects, hypertension, potassium diuresis, fluid retention, and "moon facies" were noted as side-effects in the patients treated with hydrocortisone.

Conclusions

1. Hydrocortisone, in a dosage of 100-150 mg. per day, is an effective means of achieving palliation in castrated female patients suffering from far-advanced mammary cancer.

2. A suggested mechanism of action of hydrocortisone is the depression of the adrenal-estrogen production. It is noted that estrone, estriol, and total estrogen production is decreased with the administration of hydrocortisone to castrated female patients.

3. Palliation is achieved without relation to the site of metastatic involvement.

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REFERENCES

1. Beatson, G. T.: On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases, Lancet 2:104-107; 162-165, 1896.

2. Huggins, C., and Bergenstal, D. M.: Inhibition of Human Mammary and Prostatic Cancers by Adrenalectomy, Cancer Res. 12:134-141, 1952.

3. Huggins, C.: Endocrine Methods of Treatment of Cancer of the Breast, J. Nat. Cancer Inst. 15:1-13, 1954.

4. Huggins, C., and Dao, T. L. Y.: Adrenalectomy and Oophorectomy in Treatment of Advanced Carcinoma of the Breast, J. A. M. A. 151:1388-1394, 1953.

5. MacDonald, I.: The Role of Extirpative Procedure in Cancer of the Breast, Cancer 10:805-807, 1957.

6. Cade, S.: The Role of Adrenalectomy in Cancer of the Breast, Cancer 10:777-788, 1957.

7. Taylor, S. G., III: Hormonal Modification in the Treatment of Disseminated Cancer of the Breast, Am. J. Med. 21:688-695, 1956.

8. Wilkins, L.; Lewis, R. A.; Klein, R.; Gardner, L. I.; Crigler, J. F., Jr.; Rosemberg, E., and Migeon, C. J.: Treatment of Congenital Adrenal Hyperplasia with Cortisone, J. Clin. Endocrinol. 11:1-25, 1951.

9. Forsham, P. H., and Thorn, G. W., in Textbook of Endocrinology, edited by R. H. Williams, Philadelphia, W. B. Saunders Company, 1955, pp. 222-315.

10. Lemon, H. M.; Reynolds, M. M. D., and Wotiz, H. H.: Arrest of Hormone-Dependent Cancer by Pituitary-Adrenal Inhibition, Boston M. Quart. 6:8-14, 1955.

11. Pearson, O. H.; Li, M. D.; Maclean, J. P.; Lipsett, M. B., and West, C. D.: Use of Hydrocortisone in Cancer, Ann. New York Acad. Sc. 61: 393-396, 1955.

12. Kofman, S.; Devanaboyina, N.; Buenger, R. E., and Taylor, S. G., III: The Use of Prednisolone in the Treatment of Disseminated Breast Carcinoma, Cancer 11:226-231, 1958.

13. Smith, O. W., and Smith, G. V.: Endocrinology and Related Phenomena of the Human Menstrual Cycle, in Recent Progress in Hormone Research, Proc. of the Laurentian Hormone Conference, edited by Gregory Pincus, New York, Academic Press Inc., 1952.

14. Zaffaroni, A.; Burton, R. B., and Keutmann, E. H.: The Application of Paper Chromatography to Steroid Analysis, J. Biol. Chem. 177:109-116, 1949.

15. Bloch, E.; Beerstecher, M. G., and Thompson, R.: Quantitative Study of Ketosteroids by Paper Chromatographic Methods with Applications to Human Urine, in Individual Metabolic Patterns and Human Disease: An Exploratory Study Utilizing Predominantly Paper Chromatographic Methods, University of Texas Publication 5109, Biochemical Institute Studies IV, 1951, pp. 96-108.

16. Engel, L. L.: The Biosynthesis of Estrogens, Cancer 10:711-715, 1957.

17. Lemon, H. M.; Wotiz, H. H.; Parson, L.; Sommers, S. C., and Davis, J. W.: Approaches to Chemical Pathology: Estrogen Biosynthesis in Pathologic Human Ovaries, Scientific Exhibit, 42d Clinical Congress of the American College of Surgeons, 1956.

18. Dorfman, R. I., and Ungar, F.: Metabolism of Steroid Hormones, Minneapolis, Burgess Publishing Company, 1953, Chap. 8.

19. Munson, P. L.; Goetz, F. C.; Laidlaw, J. C.; Harrison, J. H., and Thorn, G. W.: Effect of Adrenocortical Steroids on Androgen Excretion by Adrenalectomized Orchidectomized Men, J. Clin. Endocrinol. 14:495-508, 1954.

20. Dougherty, T. F., and Schneebeli, G. L.: The Use of Steroids as Anti-Inflammatory Agents, Ann. New York Acad. Sc. 61:328-348, 1955.

DISCUSSION

DR. J. B. DAVIS, Omaha: Breast cancer is the leading cause of death among women in the middle period of life and represents 21.7% of all cancers in females. Therefore, the palliative treatment of far-advanced, recurrent, and metastatic breast cancer has become a problem of major magnitude in clinical practice. It is not mysterious, then, that so many clinicians and research laboratories are studying and writing on this problem. From time to time, it is well to "take stock" of the problem, listing separately the known facts, the indefinite or suspected material, and the unknown factors.

As I see it, there are several facts which are accurate to the best of our present knowledge.

1. The ideal treatment of breast cancer is early, complete surgical extirpation.
2. Estrogens are carcinogenic agents and are responsible for the development of breast cancers in certain experimental animals.
3. Estrogens are produced by the ovaries and by the adrenal glands.
4. Many incurable breast cancers can be given worth-while palliation by hormone and hormone ablative therapy.

Among indefinite or suspected factors are these:

1. Pituitary growth hormone in an important factor in the progress and induction of human breast cancer.
2. Nucleic acids are the basic nuclear material responsible for the propagation of cancer cells.

3. Variations in α- and β-lipoproteins in normal women as compared with those in women with breast cancer indicate hormonal imbalance is a cause of breast cancer in humans.

In contrast to the two preceding lists, there are many unknown factors, two of which are (1) how to choose a suitable candidate for ovariectomy and adrenalectomy or hypophysectomy, and (2) whether medical adrenalectomy (or hypophysectomy) is equal in its palliative results to surgical ablation of these glands.

In view of the above, Dr. Block's excellent study is important for several reasons:

1. He has reemphasized that the adrenal glands are a source of estrogen in the human body.

2. He has furnished considerable additional proof supporting Huggins' theory that estrogen produced in the intact adrenals is responsible for postovariectomy exacerbations of many breast cancers.

3. He has undertaken an accurate study to determine the results of medical adrenalectomy is previously ovariectomized patients.

(*a*) If these findings prove good enough in a large series, it may be possible to save the patient the pain and expense of surgical ablative procedures.

(*b*) If the results are not adequate, it may still serve as a method of determining which patients can be benefited by adrenalectomy.

Dr. Block and his co-workers should be further congratulated on their accurate hormonal assay.

Pancreatoduodenectomy for Periampullary Carcinoma

An Evaluation of Technique, Mortality, and Results

WILBUR HILST, M.D.; CHARLES KOUCKY, M.D.; LOUIS KAUFMAN, M.D., and GERALD S. WILSON, M.D., Detroit

Pancreatoduodenectomy for periampullary carcinoma is undergoing a period of renewed interest because of the constantly increasing number of reported five-year survivors, all of whom without this surgery would be destined to an early death.[1-5] This operation, however, is a formidable one, generally associated with a high operative mortality and morbidity and low cure rate. In addition, the over-all resectability of periampullary lesions is low, even in those patients who have had symptoms for a relatively short length of time. It would appear that one of the ways to increase the number of cures would be to reduce the operative mortality in the group in which all grossly malignant tissue can be removed at the time of operation.

One of the commonest causes of operative mortality has been the high incidence of fistula formation at or near the pancreatic anastomosis.[6] With this in mind, a study of our cases of pancreatoduodenectomy was undertaken to determine the end-results and to correlate any particular method of operative technique, especially in reference to the handling of the pancreatic stump, with the morbidity and mortality rate.

Material and Methods

During the years from January, 1948, to January, 1958, a total of 49 patients underwent pancreatoduodenectomy at the Detroit Receiving Hospital of the City of Detroit and the Dearborn Veterans Administration Hospital. These operations were performed by the general surgical residents under the staff supervision of a member of the surgery department of the Wayne State University College of Medicine. Seventeen patients were from the Dearborn Veterans Administration Hospital and 32 from the Detroit Receiving Hospital. There were 28 white and 21 Negro patients, with the age distribution as seen on Table 1.

TABLE 1.—*Pancreatoduodenal Resections January, 1948-January, 1958*

Age, Yr.	No.		
20-29	2	White	28
		Negro	21
30-39	1		
40-49	9	Female	7
		Male	42
50-59	17		
60-69	13		
70 & over	7		
	49		

All but four of these patients were operated upon for some degree of obstructive jaundice. Of the four without jaundice, one had been found to have a mass in the head of the pancreas during the repair of a ventral hernia, two had previous biliary-tract-diversion procedures at other hospitals, and one was explored because of bleeding from a malignant duodenal ulcer.

The final decision as to the presence of malignancy in the periampullary area and the feasibility of a resection for cure was made by the surgeon at the time of exploration. Pancreatoduodenectomy was attempted in all cases considered by the surgeon to represent malignancy unless there were evidence of distant metastases, spread to lymph nodes outside the field of resection, or invasion of nearby vascular structures. The most difficult of these to evaluate before progressing with the operation beyond the point of no return is involvement of the superior mesenteric vein as it traverses the pancreas, and, unfortunately, in occasional instances this may be impossible to ascertain.

The basic principle of en bloc removal of the tumor was employed in all cases. As shown in Figure 1, this involves resection of the distal portion of the stomach, part or all of the duodenum, sometimes a small portion of the jejunum, the

Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 21, 1958.

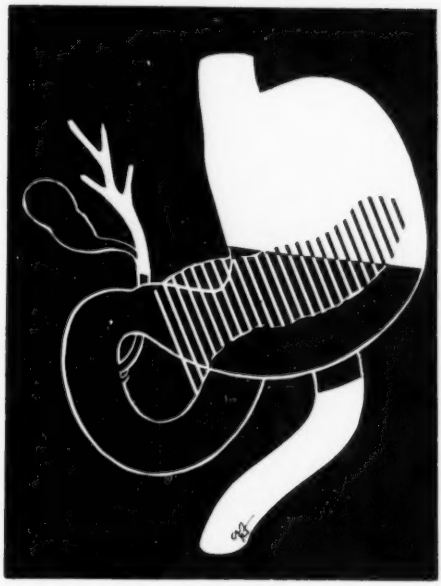

Figure 1

head or all of the pancreas, the distal end of the common bile duct, and the gallbladder. In this series an end-to-side choledochojejunostomy and a standard anterior gastroenterostomy were utilized in the reconstruction of the biliary and intestinal tracts, the gastroenterostomy site being the most distal of the anastomosis (Fig. 2). The chief variation occurred in the handling of the pancreas, when this organ was removed in its entirety (Fig. 2*a*), the distal end ligated (Fig. 2*b*), an anastomosis accomplished between the end of the pancreatic duct and the side of the jejunum (Fig. 2*c*), or the cut end of the pancreas anastomosed to the end of the jejunum (Fig. 2*d*), as popularized by Child.[7,8] In the last method, following the removal of the various anatomical structures, the distal end of the severed jejunum is delivered through the area of the ligament of Trietz, occupying much the same location as the excised duodenum. The end of the pancreas is then sutured to the jejunum, using a two-layer technique and actually inverting the pancreas into the lumen of the jejunum. The common duct and stomach are then anastomosed to the side of the jejunum, and the ligament of Trietz is reestablished.

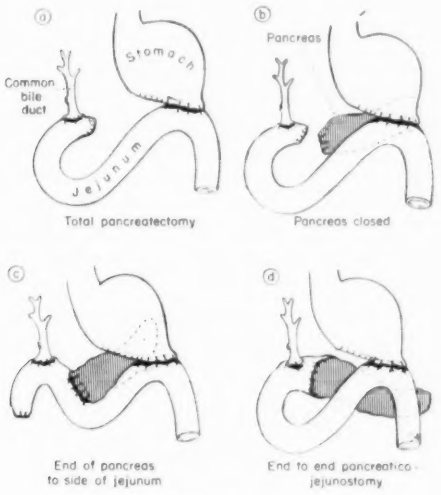

Figure 2

Results

A review of the final pathological diagnosis revealed that there were 31 instances of carcinoma of the head of the pancreas, 10 carcinomas of the ampulla of Vater, 1 carcinoma of the duodenum, 1 carcinoma of the distal common bile duct, 2 cases of adenomatous hyperplasia, and 1 granular-cell myoblastoma; in 3 instances the pathological diagnosis was chronic pancreatitis (Table 2).

TABLE 2.—*Pathological Diagnosis*

Carcinoma of pancreas	31
Carcinoma of ampulla	10
Carcinoma of duodenum	1
Carcinoma of bile duct	1
Adenomatous hyperplasia	2
Granular-cell myoblastoma	1
Chronic pancreatitis	3
Total	49

Of the 49 operative cases, 23 were considered operative mortalities in that death occurred within 30 days of operation or from complications of the procedure. In 10 instances death was due to hemorrhage, shock, anuria, or uremia. Nine deaths were due to fistula at or near the pancreatic anastomosis; and one each was due to septicemia, hepatic failure, and hypoglycemia following a total pancreatectomy (Table 3).

In correlating the operative deaths and fistula formation with the four types of reconstructive procedures used, it was

TABLE 3.—*Causes of Operative Deaths*

Shock, anuria, uremia, and hemorrhage	11
Pancreatic fistulae	9
Hypoglycemia	1
Septicemia	1
Hepatic failure	1
	23

found that in three patients on whom a total pancreatectomy was performed there were two operative deaths and, of course, no pancreatic fistulae (Table 4). In the five instances in which the pancreatic stump was closed there were four operative deaths, with two patients succumbing to pancreatic fistulae. In the 27 patients undergoing end-to-side anastomosis of the pancreatic duct to the jejunum there were 14 deaths, with 7 patients developing fistulae. In the 13 cases in which an end-to-end anastomosis of the pancreas to the jejunum was utilized there were 2 operative deaths and no fistulae—a mortality of 15%.

Twenty-six patients have survived this operation, and their subsequent course is shown in Table 5. There were 15 patients who succumbed to recurrent cancer, with an average survival of 12 months. Three patients died of intercurrent disease: Of these, one had cancer of the pancreas and died at 48 months of a bleeding marginal ulcer; the patient with granular-cell myoblastoma died at 72 months of tuberculous enteritis, and the third patient with carcinoma of the pancreas died at 7 months with a second primary carcinoma of the esophagus. At the present time eight patients are alive and well without evidence of recurrence.

TABLE 5.—*Survivorship*

Died of recurrent malignancy	15
Average length of survival, 12 mo.	
Died of intercurrent disease	3
Bleeding marginal ulcer, 48 mo.	
Tuberculous enteritis, 72 mo.	
Carcinoma of esophagus, 7 mo.	
Alive at present time	8

TABLE 4.—*Type of Reconstruction Correlated with Deaths and Fistula Formation*

	Operation		
	Cases	Deaths	Fistulae
Total pancreatectomy	3	2	0
Ligation of pancreatic stump	5	4	2
End-to-side anastomosis of pancreas to jejunum	27	14	7
End-to-end anastomosis of pancreas to jejunum	13	2	0

Thirty-one patients were operated upon prior to January, 1953, and comprise the group studied for five-year cures. In this group are one patient with carcinoma of the ampulla of Vater, living seven years; a second patient with carcinoma of the pancreas, living six years; a third patient with granular-cell myoblastoma, living five years, and a fourth patient with chronic pancreatitis, living eight years (Table 6).

Comment

One of the most difficult problems in periampullary malignancy is one's inability in the majority of cases to detect the disease in an early stage. Most cases are discovered only after obstruction to the common bile duct is evident by the onset of jaundice. By the time this has occurred the carcinoma is frequently far advanced, and resection with hope of cure may be impossible. Since it appears that little progress is being made in the direction of establishing an earlier diagnosis, one of the ways in which to increase the number of five-year survivals is to reduce the operative mortality in the small group in which cure is still a possibility.

The large number of operative deaths associated with pancreatoduodenectomy in the present series can be divided into two groups. The first group comprises the 10

TABLE 6.—*Five-Year Survivals*

Carcinoma of ampulla	7 yr.
Carcinoma, head of pancreas	6 yr.
Granular-cell myoblastoma	5 yr.
Chronic pancreatitis	8 yr.

patients dying of hemorrhage, shock, anuria, and uremia and one patient each succumbing to hypoglycemia following total pancreatectomy, hepatic failure, and septicemia. In most of these cases the operation was simply too much surgery for these usually older, debilitated, and jaundiced patients. It is felt, however, that to eliminate patients dying of these causes would mean denying the operation to many older patients for whom this is the only chance of cure.

The second group is composed of the nine patients who died as a result of pancreatic fistula. These deaths are directly attributable to technique and comprise 40% of the operative deaths. Evaluation of the four methods of handling the pancreatic stump shows that total pancreatectomy presents the advantage of having no pancreatic stump to deal with, and hence no fistula, but has the disadvantage of a possible nutritional problem from postoperative pancreatic insufficiency and the development of a very labile diabetes. Two of the three patients with total pancreatectomy in this series died in the postoperative period, one as a result of diabetes. The second method of handling the pancreas was by simply ligating the cut end of the pancreatic stump, as advocated early by Brunschwig.[9] Although diabetes does not usually occur after this maneuver, the possibility of some degree of malnutrition is still a problem. The occurrence of two pancreatic fistulae in the five instances in which this procedure was used discouraged its routine use. The method of anastomosing the cut end of the pancreatic duct to the side of the jejunum, although presenting sometimes a difficult technical feat, has the advantage of preserving both the enzymatic and the hormonal output of the pancreas. Of the 27 patients undergoing this procedure, however, 7 developed fatal pancreatic fistulae. An end-to-end anastomosis of the jejunum to the pancreas, as advocated by Child, likewise preserves the endocrine and hormonal output of the pancreas. This method has been utilized by us almost exclusively in the last four years, resulting in only 2 deaths in the last 13 cases and no fistula formation. We have found this latter maneuver to be a relatively simple technical procedure and believe it has added materially to lowering the operative mortality through minimizing the danger of fistula formation.

Although the operation has been utilized only in instances in which the operating surgeon was of the impression that the underlying disease was cancer, the final pathological diagnoses in three instances was chronic pancreatitis, an error of 6%. Concerning the problem of confusing benign and malignant disease of the head of the pancreas, it has been the philosophy of the surgery department of the Wayne State University College of Medicine to proceed with the operation on the basis of clinical impression of malignancy, realizing, like Brunschwig [1] and others, that there will be a 7% to 10% error in diagnosis on the side of removing benign for malignant disease. Unfortunately, histological diagnosis by frozen section is unreliable because of the pancreatitis surrounding a central core of neoplasm, too often giving a false-negative report. We share the opinion of those who would rather do a resection in an occasional case with benign disease than deny the operation to the substantial number of patients in whom histological diagnosis cannot be established.

The two five-year cures reported here, one of the ampulla of Vater and one of the head of the pancreas, combined with other reported cures, have established the curability of this otherwise hopeless disease. The improvement in operative mortality to an acceptable level, combined with the greater experience gained by a large number of surgeons, is a step toward increasing the number of cures and should help overcome the reluctance of many to use this operation in cases of cancer of the head of the pancreas.

Summary

The experience with 49 cases of pancreatoduodenal resection over a nine-year period at the Detroit Receiving Hospital and

the Dearborn Veterans Administration Hospital is presented.

Although the over-all surgical mortality of pancreatoduodenal resection in this series was 47%, the recently employed procedure of end-to-end anastomosis of the pancreas to the jejunum has resulted in a 15% mortality.

Two five-year survivals of cancer are reported: one of cancer of the ampulla of Vater, and the second of cancer of the head of the pancreas.

It is our opinion that with the present operation the mortality rate has been decreased to an acceptable level, and that there can be an appreciable salvage rate for cancer in this area.

Wayne State University College of Medicine.

REFERENCES

1. Brunschwig, A.: Pancreatoduodenectomy: A "Curative" Operation for Malignant Neoplasms in the Pancreatoduodenal Region; Report of 3- Over 5-Year Survivors, Ann. Surg. 136:610, 1952; Tr. Am. Surg. A. 70:273, 1952.

2. Dennis, C., and Varco, R. L.: Survival for More Than 5 Years After Pancreatoduodenectomy for Cancers of the Ampulla and Pancreatic Head, Surgery 39:92, 1956.

3. Pratt, J. H., and Welch, J. S.: Carcinoma of the Head of the Pancreas, Long-Term Survival, A. M. A. Arch. Surg. 72:500, 1956.

4. Kaufman, L. W., and Wilson, G. S.: Carcinoma of the Head of the Pancreas and Periampullary Region, Am. J. M. Sc. 230:201, 1955.

5. Porter, M. R.: Carcinoma of the Pancreatico-Duodenal Area: Operability and Choice of Procedure, Ann. Surg. 148:711, 1958.

6. Cattell, R. B., and Warren, K. W.: Surgery of the Pancreas, Philadelphia, W. B. Saunders Company, 1953.

7. Child, C. G., III: Pancreaticojejunostomy and Other Problems Associated with the Surgical Management of Carcinoma Involving the Head of the Pancreas: Report of 5 Additional Cases of Radical Pancreaticoduodenectomy, Ann. Surg. 119: 845, 1944.

8. Child, C. G., III: Radical One-Stage Pancreaticoduodenectomy, Surgery 23:492, 1948.

9. Brunschwig, A.: Surgery of Pancreatic Tumors, St. Louis, C. V. Mosby Company, 1942.

DISCUSSION

DR. GROSVENOR T. ROOT, Oakland, Calif.: It is encouraging to have even a slight note of optimism in a discussion of carcinoma of the head of the pancreas. I am confident that the morbidity and mortality due to leakage at the pancreatic anastomosis will be markedly decreased if attention is paid to the technical details stressed by Dr. Hilst. I should like to discuss briefly a case in which my partner, Dr. Burt Christensen, and I operated several years ago. In fact, if the patient continues to enjoy his present excellent health until next March, he will have lived 10 years from the time of his operation; for it was nearly 10 years ago, in March, 1949, that we operated upon this 63-year-old man for an obstructing lesion of the second portion of the duodenum (Slide). The patient was not jaundiced, and the probe may be seen in the ampulla and extending up an entirely normal common duct (Slide). On cut section and subsequent microscopic examination, the lesion was found to be a carcinoma of the head of the pancreas, directly invading the wall of the duodenum. Interestingly enough, at the time of surgery the patient was found to have a hard mass filling the caudate lobe of the liver. This was resected, and frozen-section examination revealed the lesion to be a hemangioma. We proceeded with the one-stage Whipple procedure, directly anastamosing the pancreas with the end of the jejunum. It is the occasional long-time follow-up, such as in this case, that allows us all to have some optimism regarding this condition. There is no doubt that this patient's survival depended entirely upon a complete resection of his lesion.

DR. GERALD WILSON, Detroit: There are a number of problems confronting the surgeon in dealing with carcinoma of the periampullary area. The first of these is establishing a preoperative diagnosis. Frequently there is a high index of suspicion that tumor is present; but, by and large, the operation is performed because of obstructive jaundice. This was true in all patients in the present series except for two who had previous biliary-tract-diversion procedures at other hospitals, and one patient who was found to have cancer on routine abdominal exploration incidental to the repair of a ventral hernia. Another problem is that of distinguishing between benign and malignant disease in lesions of the pancreatic head. As you saw, we have a 6% error in confusing pancreatitis

for carcinoma. Perhaps pancreatitis is not altogether a benign disease, however; and if the mortality rate for this operation can be reduced to an acceptable level, this operation for pancreatitis may not constitute too serious an error. Another problem is evaluating the resectability for cure in pancreatic cancer. In an occasional instance in this series the lesion seemed to have been totally excised except for adherence to the portal vein. As Dr. Hilst pointed out, the standardization of the procedure, particularly the handling of the pancreas, seems to have reduced our operative mortality to fairly acceptable levels. Since this article was written, we have had six additional resections, without a death. Finally, there is the problem of our curability of cancer in this area. Our cure rate is nothing to boast of; but, as Dr. Hilst stated, we believe we can increase the salvage rate in our hospital by reducing the operative mortality to a minimum.

DR. CHARLES G. JOHNSON, Detroit: I am a little surprised that everyone has been so nice; usually when one talks about carcinoma of the pancreas and resection, one finds a great deal of discussion, because the trend in many areas is away from doing these rather major procedures. We have still maintained that the procedure is worth while. We maintain it on the basis that the patient who has a carcinoma of the head of the pancreas is looking down the business end of the barrel anyway; he is going to be uncomfortable; he has nothing to lose and a lot to gain if you give him a little palliation. These patients, even though they have recurrences and difficulties, usually are somewhat better after the operation, unless they succumb rather promptly to it. It is good for my soul to point out that in most of these early cases I supervised the operative procedure myself, and for many years I was an advocate of transplantation of the pancreatic duct into the duodenum, because I felt it was more physiological and could be done. I have more recently ascribed to the present procedure, quite obviously. In these cases the operations were all done by residents; and residents do not stay long enough for the one resident to do them all. Most of them have been done by different persons. Likewise, the cases have been staffed by different physicians. The whole problem, I believe, needs reconsideration, for I think there are still large numbers of these patients who merit an operative procedure. We should not be too pessimistic about it, for I think we are still making progress in this area, even though it seems rather slow. I hope the next 10 years will be a lot better than the past 10 years.

DR. CHARLES PUESTOW, Chicago: When Dr. Johnson passed me in the aisle just now, he asked me if I would discuss this paper. A number of years ago, Dr. Will Mayo reported on a large series of patients who had had short-circuiting operations for obstruction of the bile ducts, supposedly due to carcinoma of the pancreas; 15% lived out their normal life expectancy, indicating that the obstruction probably was on the basis of chronic pancreatitis. If I interpret correctly the statistics given today, there were three patients with chronic pancreatitis operated on, and one with a five-year survival had chronic pancreatitis; something, therefore, must have happened to the other two. Two patients with carcinoma were saved, one for six and the other for seven years. Of course, we do not know whether or not these people are going to be dead by next year of metastases. I should like to ask what there was about the value to society of the two patients with carcinoma, and why it was advisable to save them at the sacrifice of the two patients with pancreatitis. That is a little facetious. I think the operation deserves a lot more study and use, and I believe we shall improve results. I certainly am in favor of the implantation of the head of the pancreas into the jejunum rather than attempt a mucosa-to-mucosa anastomosis, which I believe is not a satisfactory operation. I should like to make one other comment. Dr. Gillesby suggested to me last week that when we operate on a patient with carcinoma of the head of the pancreas who undoubtedly has a pancreatic-duct obstruction, and when we do find an inoperable lesion, we should cut off a little of the tail of the pancreas and do a pancreatojejunostomy of the Roux en-Y type, in addition to a biliary short-circuiting operation. We may make these patients more comfortable by permitting free pancreatic drainage into the intestine, and may increase their survival, as well as their comfort.

DR. DEWARD O. FERRIS, Rochester, Minn.: We, too, feel that we must not take a defeatist attitude in regard to carcinoma of the pancreas. If the disease seems limited to the pancreas, we advise and perform pancreatoduodenectomy, but not before we have confirmed the diagnosis by microscopic study. Our surgical pathologists, using the frozen-section technique, can accurately evaluate the specimens we obtain from the pancreas. However, it is up to the surgeon to secure a representative specimen. It has been our

experience that the specimens removed by the Silverman needle are preferable to those removed by scalpel. With the needle, multiple specimens may be readily obtained more accurately and with less disturbance to the pancreas. In our experience, the use of the Silverman needle to obtain specimens of the diseased pancreas has been a very satisfactory procedure.

DR. WILLIAM J. GILLESBY, Hines, Ill.: This demonstrates the error of not reporting bad results, as well as good ones. Dr. Ferris has mentioned the use of Silverman-needle biopsies in the pancreas. We started doing transduodenal Silverman-needle biopsies of the pancreas three or four years ago and ran a series of some 12 or 13. We obtained excellent pieces of tissue, and then had two cases of fatal acute hemorrhagic pancreatitis. Dr. Ferris has been lucky. We were not so lucky.

DR. WILBUR HILST, Detroit: We should like to thank Drs. Smith, Root, Ferris, and Gillesby for their comments. Dr. Puestow questioned the statistics of the advantage of the operation, but directed his remarks to Dr. Johnston. I am going to let them discuss that during the cocktail hour.

MR. RODNEY SMITH, London, England: I should like to say how much I appreciate being asked to this fine meeting. I have greatly enjoyed the entire afternoon, and this most interesting paper on a subject which has been of considerable interest to me.

During the last 13 years I, myself, have explored 230 of these lesions and have resected 60 of them. Fifty-six patients survived surgery, but the later results depended on the type of lesion. (Slide) I would particularly like you to look at this x-ray, from a woman with a lesion ulcerating into the second part of the duodenum. Symptoms had been present for 18 months. Her x-ray was, unfortunately, reported as being normal, and she was sent home. She finally came to us 18 months after that. (Slide) She now had this more extensive lesion. This was three years after her first symptoms, and at laparotomy she, nevertheless, still had a resectable lesion and is today in good health, four and one-half years after pancreatoduodenectomy. I show this to indicate how very slow growing some of these lesions are, and therefore how well worth while it is to resect them.

(Slide) At the other end of the scale, this is an operative picture of a different sort of pancreatic tumor altogether. Nevertheless, even a vast tumor of this kind can sometimes be resected, and symptomatically with profit, even though the long-term outlook is very poor.

(Slide) A few technical tricks with x-rays. We have used at St. George's Hospital transhepatic cholangiography in an occasional case of obstructive jaundice.

(Slide) A little barium given at the same time may allow one to outline the extent of a tumor. Here is a blocked common duct; here is the duodenum, and one can see that there is, in this case, a large tumor, and certainly not an ampullary one.

We have found this technique useful in a small group of cases, although there is a risk of leakage of bile when the needle is taken out. This is a very real risk.

One other form of x-ray which we have sometimes adopted can be interesting in studying what happens to the vastly dilated bile passages after pancreatectomy and anastomosis of the common duct to the intestinal tract. It is not easy to take an accurate picture, but we found that a most effective contrast medium as well as one of the cheaper ones, is easily obtainable, and we now do a Pepsi-Colagram on these patients. (Slide) In this technique we shake up a bottle of Pepsi-Cola and make the patient drink it while it fizzes. The patient is forbidden under any circumstances to burp, and we then take a picture of him standing up, and we get a very fine outline of the bile passages. Here is the anastomosis between the biliary tree and the jejunum clearly outlined by getting a little gas into the small intestine. It is interesting to see how very quickly the enormous dilatation settles down that is present in all these cancer patients.

As regards the final outcome in this type of cancer, my experience has been the same as anybody else's, and that is that it is well worth while resecting these lesions for primary carcinoma of the duodenum or ampullary carcinoma. I have recently reported six five-year survivals after pancreatectomy. One patient had a cyst-adenocarcinoma (which was a different tumor altogether). Five were ampullary or duodenal carcinomas. I have had no patient with carcinoma of the pancreas proper who has gone five years as yet. So I feel one can be reasonably optimistic about ampullary tumors, if technically resectable. As regards carcinomas of the pancreas proper, however, we might conclude with a quotation from Sir Winston Churchill. One of his famous phrases sums up the whole business. He was talking in this country about Mr. Atlee. Someone asked him what Mr. Atlee was like, and his reply was: "Well, he is a nice, modest little man." He thought for a bit and added: "Mind you, he has much to be modest about."

Simultaneous Repair of Mitral and Tricuspid Valves Through Right Atrium and Interatrial Septum

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Secondary tricuspid regurgitation is frequently responsible for serious downgrading of the clinical status of patients whose only primary rheumatic valvular lesion is of the mitral valve. In some instances the signs of tricuspid insufficiency disappear during the period of medical preparation for standard mitral commissurotomy. In others the disturbed dynamics which result from the tricuspid failure cannot be reversed and the patient must be operated upon for the mitral lesion in spite of the defect. If sufficient benefit accrues from the surgery to diminish right-heart work load, the tricuspid ring shrinks as right ventricular distention disappears. Tricuspid valvular sufficiency then results as a more or less delayed benefit of mitral valve commissurotomy or repair. The question arises as to whether repair of the tricuspid regurgitation accomplished at the same time as repair or commissurotomy of the mitral valve would be beneficial in terms of providing more rapid and certain improvement in cardiac competency. The technique and results obtained in a small series in which repair of the tricuspid valve was done are to be presented in exploration of the idea that tricuspid regurgitation is an indication for open mitral surgery.

Some tentative indications for the use of open, rather than closed, approach to the mitral valve are emerging. Owing to general dissatisfaction with blind methods of handling mitral regurgitation, the presence of a regurgitant element is the clearest indication. Evaluation of the individual patient in regard to the existence of a dynamically significant degree of regurgitation accompanying mitral stenosis is not a simple, direct matter. The presence and character of an apical systolic murmur is a poor indication. In a group of 124 patients studied for correlation between the presence of this murmur and the discovery at surgery of a systolic "jet" through the mitral orifice, it was found that correlation existed in 89 of the cases and failed to exist in 35.[1] The 35 instances in which there was no correlation included 23 in which a significant murmur was found but no jet could be demonstrated and 12 having a palpable jet and significant regurgitation without the physical finding of the systolic murmur. On the basis of this study, if open-heart approach to the mitral valve were applied on the indication that mitral regurgitation was present because of the finding of a significant murmur, 23 patients without regurgitation would have been subjected to open surgery unnecessarily. Also, 12 patients would have been missed as candidates for open repair of the valve.

A demonstrable degree of left ventricular enlargement in the absence of aortic valve pathology was found, in the same study, to be a significant indication of mitral insufficiency. Right heart catheterization with pulmonary capillary wedge pressure tracings offers some indication of the degree of mitral regurgitation, as do the left atrial pressure tracings and dye-dilution curves of left heart catheterization. However, no

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amount of careful preoperative study seems completely to succeed in evaluating the presence and degree of regurgitation accompanying mitral stenosis. On this basis, we are perhaps on the way to the routine application of open methods to all surgery for mitral disease. Present risk and magnitude of the personnel and supply problems of cardiopulmonary bypass inhibit this step now.

A second indication for open approach to the mitral valve exists in relation to reoperation on patients whose symptomatology has recurred after a mitral commissurotomy by closed methods. It is probable that several types of valves should be reoperated upon under direct vision, some by another blind commissurotomy, and some should not be subjected to a second operation. Reoperation using cardiopulmonary bypass appears to us now to be needed in patients who benefited temporarily by a partially satisfactory commissurotomy on a tough fibrotic valve. In such valves, which resist complete finger dissection of either commissure, we have been inhibited in thorough cutting in the commissure by difficulty in landmark identification and fear of production of disastrous regurgitation. The modest enlargement obtained produces improvement, which may not last. There being no reason to suppose that a second blind procedure would be more complete, commissurotomy under vision is advisable. Reoperation provides another indication for open commissurotomy in instances of production of mitral regurgitation in the previous operation. Open repair will sometimes be immediately necessary when the regurgitation is serious. Often such a primary operation will provide a period during which the patient is benefited by the relief of the stenosis before the regurgitation produces its deleterious effect.

Reoperation, repeating the initial closed commissurotomy, is suggested when refusion is suspected of cusps which were satisfactorily separated at the first procedure. This indication depends on the reliance which every surgeon should be able to place on his observations at surgery and the objectivity of the report of the first operation.

Certain observations made at the initial commissurotomy should, we believe, be contraindications to any form of second operation now available. Outstanding in this group is the finding of a heavily calcified and contracted valve mechanism. It is occasionally possible to improve flow through such valves, but rarely is the benefit lasting. Perhaps open repair of these valves after recurrence of symptoms should wait for the development of prostheses permitting total replacement of the structure.

Clots within the chamber of the left atrium would, if their existence could be known, be clear indication for open mitral procedures. The ease and completeness with which they can be aspirated when the left atrium is open and dry removes all risk of subsequent detachment and formation of emboli by these particular clots. No one has suggested that a history of previous peripheral arterial emboli indicates that clots are present at the time of a commissurotomy. Our own unpublished data on this relationship suggest that there is no correlation between previous emboli and either the danger of emboli complicating a blind commissurotomy or the discoverable presence of atrial thrombi at operation. Two types of cases have been subjected to open commissurotomy because of the thrombus problem. Calcification of portions of the lateral and superior left-atrial wall can be strongly suspected of being accompanied by detachable mural thrombi. The second, commoner indication of the presence of thrombi is their discovery on external palpation of the left atrium upon exposure from the left side during the approach for routine commissurotomy. Prior to application of cardiopulmonary bypass to mitral surgery, we handled this disturbing problem by various attempts to aspirate or withdraw the thrombi through the atrial appendage. At the same time, we persisted in performing the planned operation. Since we have used open methods, however, this finding during rou-

tine operation has been made twice. In both cases, the planned procedure was abandoned, and the patient was prepared for later open left atriotomy under bypass. In each case at the second procedure clots were easily and completely removed. For a variety of obvious reasons, the use of a thrombosed atrium as an indication for open surgery is almost impossible. Even clots being found at commissurotomy are not too helpful, because they will usually not be noticed until palpated by the finger already introduced into the atrium.

TABLE 1.—*Catheterization Data*

Case No.	RA	RV	PA	Wedge	Output, L.	Resistance
1	15/10	50/9	50/30	(12)	2.77	615
2	(7)	56/6	56/33	(26)	4.25	845
3	Not catheterized — advanced risk					
4	Not catheterized					
5	11/6	90/6	90/30	..	2.40	2,000
6	20/10	85/20	85/40	..	1.70	3,000
7	(11)	..	85/41	(38)	5.36	839
8	Not catheterized — advanced risk					

Clinical Material

In our present series of open operations for correction of acquired valvular defects, eight patients have been subjected to a tricuspid-annulus-plication procedure at the same time that the mitral value was operated upon (Table 1). The tricuspid insufficiency in each case was severe and would not entirely remit during medical management. There were three patients in whom the mitral lesion was purely one of insufficiency, two in whom the mitral valve was stenotic, and three having a combined mitral stenosis and insufficiency.

All eight patients were in Class III or IV on the basis of their cardiac status during optimum medical management. There have been four deaths in this series of eight patients.

Six of the eight patients were subjected to preoperative cardiac catheterization. In two the severe degree of the mitral and tricuspid disease made catheterization for anatomical diagnosis unnecessary. Postoperative catheterization has not yet been carried out on any of these patients, and the clinical results must be judged at this time on the functional capacity, physical signs, and roentgenologic evidence of changes in cardiac size and shape.

Technique

The accepted *incision and approach* to the mitral valve through a right thoracotomy for left atriotomy using cardiopulmonary bypass was utilized in seven of eight cases. The posterolateral incision was used, with extension to the costochondral junction anteriorly. In these patients, however, in order to carry out tricuspid valve repair as a part of the mitral procedure, the approach was made through the lateral wall of the right atrium, with subsequent exposure of the mitral valve through an incision in the interatrial septum. This approach was described by Effler [2] and offers a direct and apparently safe exposure of the valve.

In one of the operations this exposure was varied in that the incision into the thorax was through a median sternotomy. This patient had the highest calculated pulmonary vascular resistance in the series and a high pulmonary-artery pressure. The median sternotomy was used for the major reason indicated in a previous description of its use and indications in open heart surgery,[3] i. e., avoidance of opening the pleural space in the presence of severe pulmonary vascular changes. On the basis of this single case, one of the patients who succumbed to the procedure, it is possible to say that the median sternotomy affords clear visualization of the mitral valve through the right atrium and the interatrial septum but would not be adequate for approach to the mitral valve through the right side of the left atrium unless the atrium were markedly enlarged, due to mitral insufficiency.

Potassium cardiac arrest was induced in each of the eight operations by the rapid injection of 2.5% solution in blood of potassium citrate into the root of the aorta proximal to an occluding clamp, placed after balanced cardiopulmonary bypass had been established. The amount of solution required has been minimized by rapid injection. It varied in this series from 6 to 20 ml. Entrance of the potassium-containing blood into the lung is prevented by immediate obstruction of the pulmonary artery and decompression of the right atrium by simultaneous beginning of the right-atrial incision.

The *extracorporeal circuit* consists of a vertical cylinder bubble-diffusion oxygenator designed in the department of surgery of the University of Illinois. The oxygenator design permits the use of a variety of bubble-diffusion chambers giving proper oxygen and carbon dioxide exchange for the flow calculated to be required for each individual case. Perfusion rates of 80-100 ml. per kilogram of body weight per minute were used.

Removal of blood from the superior and inferior venae cavae was by active pumping rather than gravity drainage. Right-angle stainless steel catheters of proper length were used in order to free a maximum area of the right atrial wall for the incision. Both femoral arteries were cannulated for arterial return through plastic catheters of the maximum size conveniently tolerated by the vessel lumen. This utilization of two arteries for arterial supply is presently rou-

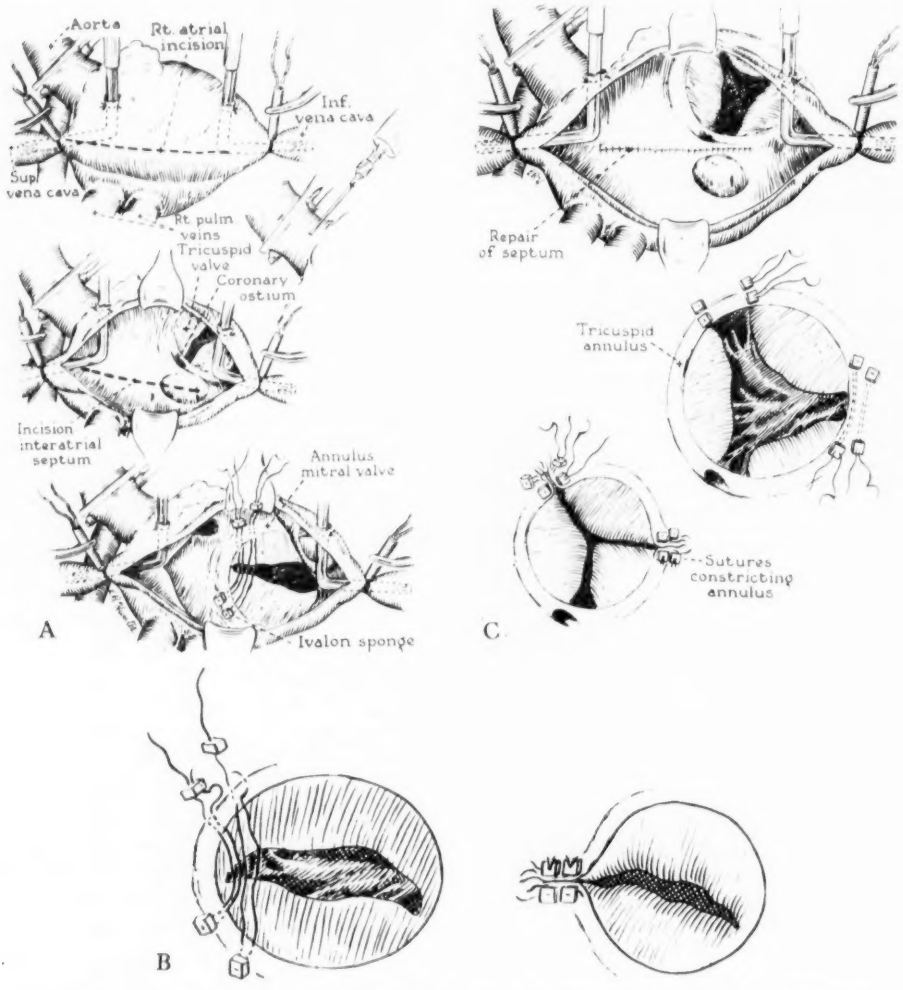


Fig. 1.—*A*, incisions in the lateral wall of the right atrium and through the interatrial septum. The insert indicates the injection of potassium citrate solution into the proximal aorta. *B*, enlarged detail of the method of placing plicating sutures in the mitral annulus at the posterior commissure. *C*, plication at two commissures of the tricuspid annulus.

tine in all perfusions substituting for the previously reported attachment of a temporary graft end-to-side to the ascending aorta for this purpose. Two catheters, rather than one, provide a maximum orifice for arterial return, diminishing pumping pressure and trauma to blood.

The *approach and standard method of repair* of both valves is illustrated in the semidiagrammatic drawings (Fig. 1*A*, *B*, *C*). After establishing the extracorporeal circuit and inducing cardioplegia, the incision already started in the right atrium is enlarged and the interior of the right atrium observed. The interatrial septum is immediately opened for a small distance in the region of the foramen ovale for decompression of the left atrium. Plication of the tricuspid annulus is then carried out at two commissures, using two or three sutures placed through polyvinyl formalinized (Ivalon) sponge pledgets at each commissure. The suture is passed through the strong fibrous tissue of the ring rather than the base of the valve leaflet. A valve-ring circumference admitting four fingers beyond the distal interphalangeal joint is sought. The ability of the valve tissue to cover this orifice can be demonstrated by approximating the leaflets with small hooks and tissue forceps.

The incision in the interatrial septum is then extended using scissors, the extent and direction of the incision being controlled by observation of the left atrial side to avoid carrying the incision outside the heart at the superior interatrial groove. In the repair of pure mitral regurgitation the posterior commissure has been selected as the site of annular plication. The amount of plication was judged by the degree of loss of substance of the leaflets and the apparent dilatation of the valve ring. The handicap of cardioplegia prevents direct observation of the valve in motion to determine when competency has been obtained. Lifting the leaflets into closed position has been substituted.

The restoration of a stenotic valve is extremely satisfactory using the landmarks of the chordae insertions as guides to the direction of the commissures, which are not always obvious from the structure of the upper surface of the stenosed leaflets. The combination of stenosis and regurgitation has not proved trying in the eight cases in the present series. Complete freeing of the commissures is followed by a suitable degree of plication of the annulus. Severe loss of valve substance, surgically produced regurgitation, and serious degrees of calcification have not been encountered in these combined tricuspid and mitral procedures. Various techniques used in other cases, and described by Kay,[4] are anticipated sometimes to be necessary.

Maximum care is exercised in closure of the septal incision using a continuous silk suture reinforced by interrupted sutures. The low pressure difference between the two sides of the incision makes it unlikely that a septal defect will result. In the stationary heart it is unnecessary to aspirate the left ventricle during the procedure. Foam is not present because the heart is quiet. The blood returning to the heart through the pulmonary veins fills the left atrium and ventricle as needed during the period of closure of the septum.

Routine closure of the lateral wall of the right atrium coincides with removal of the clamp from the aorta, allowing coronary perfusion. After removal and discard of a suitable amount of the potassium-bearing coronary sinus blood, the right atrium and ventricle are allowed to fill. Since the left atrium is not decompressed after the interatrial septum has been repaired, either aspiration of coronary blood is continued through a remaining small defect in the right atrial wall or one of the caval-occluding tapes is removed for decompression until cardiac action satisfactory for stopping the perfusion is observed. Five hearts have started in sinus rhythm or rhythm of auricular fibrillation and thereafter maintained the rhythm. One started in auricular fibrillation and passed into uncontrollable ventricular fibrillation. Two started in ventricular fibrillation, both being restored to

sinus rhythm with application of electrical shock.

Results

Of the eight patients subjected to this combined procedure (Table 2), one (Case 8) succumbed to uncontrollable ventricular fibrillation, which had its onset several minutes after restoration of cardiac action in auricular fibrillation. A second immediate death occurred in the patient (Case 6) having the highest pulmonary vascular resistance secondary to pulmonary changes. The cardiac output in this patient at rest was calculated at 1.7 liters per minute. After repair of both valves this heart was immediately restored to auricular fibrillation. The pulmonary artery pressure was observed to mount steadily, while the aortic pressure failed to be supported. The heart stopped in an atonic state, from which it could not be resuscitated. The mitral lesion in this case was a combination of mitral stenosis and regurgitation with preponderant stenosis. The case is an example of poor selection for any kind of surgical intervention in spite of poor medical prognosis. It also raises the question as to the routine advisability of producing acute competency of the tricuspid valve in cases having significant degrees of pulmonary vascular resistance.

TABLE 2.—*Results of Combined Mitral-Tricuspid Valve Repair*

Case No.	Class	Lesions	Result
1	III	MS-TI	Upgraded to good Class II; fully employed (12 mo.)
2	III	MS-TI	Class II; normal housekeeping (5 mo.)
3	IV	MI-TI	Class II; no symptoms, on still restricted activity (4 mo.)
4	III	MI-TI	Class II; no symptoms, normal housework (8 mo.)
5	III	MS-TI	Improved cardiac action; late death, infection
6	III	MS-MI-TI	Advanced pulmonary vascular change; immediate death
7	IV	MS-MI-TI	Cardiac cirrhosis; failure to heal; late death
8	IV	MI-TI	Ventricular fibrillation; immediate death

Two late deaths have occurred, one 40 days and one 70 days after surgery. The first of these was that of a woman (Case 5), 50 years of age, having tight stenosis as the mitral lesion. A very satisfactory anatomical result was obtained in both valves. The early postoperative course was excellent and included the observation that the apical systolic murmur was abolished and the murmur of mitral valve stenosis was markedly softened. A wound infection developed, from which Staphylococcus aureus and Pseudomonas aeruginosa organisms were cultured, and maximum antibiotic therapy was established. The febrile course was slow to terminate, and the antibiotics were continued into a dangerous period. At autopsy, 40 days after surgery, no sign of infection remained.

The second late death was that of a man (Case 7), aged 43, having severe tricuspid and mitral insufficiency. Marked changes in liver function were known to be present, secondary to the long-standing cardiac problem. Healing of the chest wound was delayed; infection was a problem for some weeks. Some improvement in right-heart function, in reduction in peripheral venous pressure, seemed to be present soon after surgery. The patient died after a long febrile course, marked by recurrence of accentuated signs of right-heart failure. Autopsy showed a failure of healing of both plication areas, with cutting through of the sutures and breakdown of the repair.

The four remaining patients listed in Table 2 presently show results 2 to 12 months following surgery. Significant improvement has been observed in each in cardiac size and contour, as seen in x-rays (Figs. 2, 3, and 4). The clinical improvement in exercise tolerance is significant in each and is tabulated. Changes in physical signs, including liver size and pulsation, venous pressure and pulsation, and softening or disappearance of the murmurs, are most satisfactory aspects of the follow-up.

Comment

General Value of Concomitant Tricuspid Repair in Mitral Disease.—In planning this

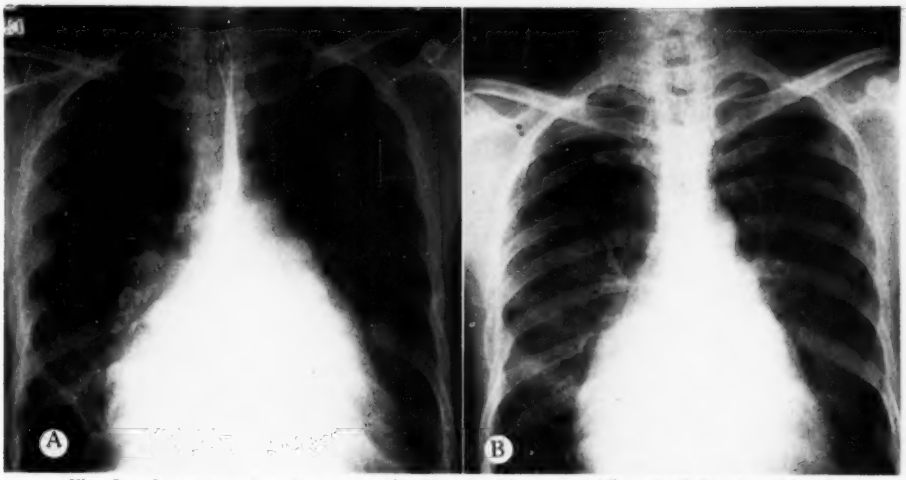
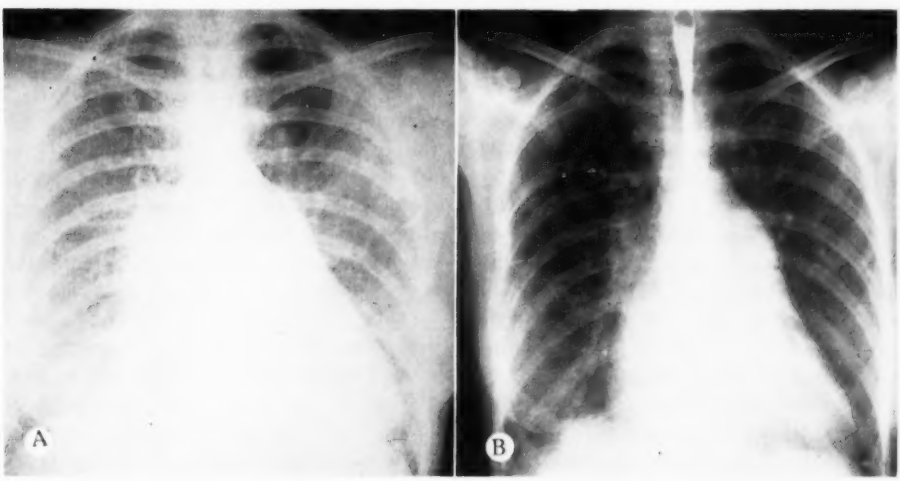


Fig. 2.—*A*, preoperative chest x-ray in 44-year-old woman (Case 1, Table 2) with mitral stenosis and intractable tricuspid insufficiency. *B*, chest x-ray eight months following repair.

double valvular repair, consideration was given to the possibility that surgically induced acute tricuspid competency might be deleterious rather than helpful. The question revolves about the ability of the strained and hypertrophic right ventricle to combat the resistance of the pulmonary circuit in the sudden absence of tricuspid regurgitation, which might be imagined to be a functioning safety valve. The resistance of the pulmonary circuit is the sum of pulmonary vascular resistance plus the obstruction offered by the stenotic or regurgitant mitral valve. Superficially, since the mitral element should be improved, it appears that the severity of the pulmonary change, either irreversible or not immediately improved, would govern the result. In one patient exhibiting severe pulmonary vascular resistance preoperatively this particular factor may have led to disaster.

In the absence of anatomical pulmonary arterial change the improvement in right ventricular efficiency resulting from acute

Fig. 3.—*A*, preoperative chest x-ray in 38-year-old woman (Case 2) with mitral stenosis and tricuspid insufficiency. *B*, chest x-ray five months after surgical repair.



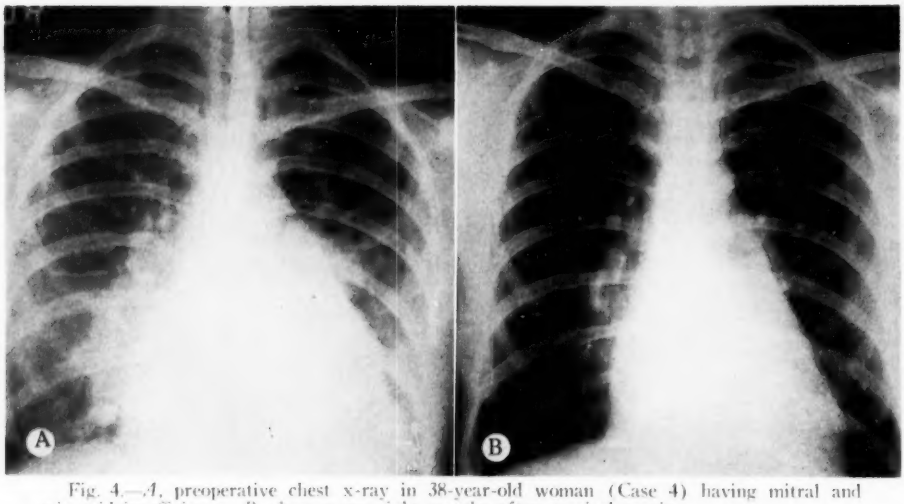


Fig. 4.—*A*, preoperative chest x-ray in 38-year-old woman (Case 4) having mitral and tricuspid insufficiency. *B*, chest x-ray eight months after surgical repair.

competency of the valve should be markedly beneficial. One patient in this series was notable for resistance to all forms of diuresis to clear generalized water retention. The excretion of sodium in this patient was measured over individual 24-hour periods before surgery, during the surgical period of several days, and thereafter for 3 days. Within 12 hours of surgery the sodium excretion abruptly increased, together with a marked diuresis, which cleared excess body water before the few postoperative days of observation were completed. This patient (Case 4) has followed an extremely satisfactory course. The sodium excretion and diuresis appeared dramatically after surgery, in our opinion, because of the acute competency of the tricuspid valve.

Approach Through the Right Atrium.—The mitral valve is far more accessible through the interatrial septum than through the left atrial wall approached through the right chest. This is particularly true when the mitral lesion is one of stenosis, in which case the left atrium is likely to be small, rather than enlarged, as in mitral regurgitation. The cardiac conduction system is not subjected to any danger by a septal incision passing through the foramen ovale. Failure of the septal incision to heal is hardly to be anticipated, because there is essentially no stress of pressure difference. In the patient (Case 7) previously discussed as showing a poor ability to heal, possibly due to liver damage, the interatrial septal incision was united.

The possibility of substituting a sternum-splitting incision for the right thoracotomy was raised. When tried in one of the present series of operations, it was found to afford an excellent approach to the valves. Some forward rotation of the base of the heart was necessary. This could probably not be accomplished so safely in the absence of cardiac arrest. Air displacement from the ventricles might be less efficient with the patient in the supine than in the right decubitus position.

Use of Cardiac Arrest.—Cardiac arrest provides a quiet operative field and allows for easy retraction and rotation of the heart where this is desirable. It prevents ejection of blood-air mixture into the aorta from the left ventricle at the moment that the mitral valve is made competent. We believe there is no question that the left ventricle if properly filled can eject against the extracorporeal-pump pressure. The danger would seem even more real in view of the fact that the mixture is agitated by ventricular action, producing actual foam. In the quiet heart air within the left ventricle

is far more easily removed because it levels without forced mixing with the dependent layer of blood.

The disadvantages of use of arrest consist of the possibilities of chemical damage to the diseased myocardium and the loss of a visible end-point in the repair of either the mitral or the tricuspid regurgitation.

We cannot express an opinion in the comparison of the use of arrest and operations on the valves during cardiac action. It must be pointed out that Kay,[4] Effler,[2] and Lillihei[5] express satisfaction with the latter technique.

High-Flow, Atraumatic, "Balanced" Perfusion.—The value of perfusion rates in adults of 75 ml/kg/min. or in excess of that amount cannot be evidenced by this segment of our perfusion experience. The rapid restoration of organized ventricular contractions upon removal of potassium from the coronary bed by a rapid perfusion in the great majority of cases is a benefit of high flow which should be stressed. The use of a large total cross-section area in the arterial return to the patient by cannulation of both femoral arteries reduces the trauma to blood and allows for flows in excess of 5 liters per minute without requiring high pump pressure to force blood into the artery through a smaller orifice.

The "gas-balanced" perfusion obtained through varying the size of oxygenation chambers in proportion to the minute volume of the anticipated demand results in a normal level of external respiration and an unchanged oxygen, carbon dioxide, and pH level in the blood.

Selection of Patients.—On the basis of this small experience with simultaneous repair of the tricuspid valve during mitral valve surgery, it is suggested that unremitting tricuspid insufficiency is an additional indication for open mitral surgery, as opposed to closed commissurotomy in mitral stenosis. Also, when open repair is required of the mitral valve for regurgitation, concomitant tricuspid repair should be done.

Because of the somewhat greater trauma of the double intracardiac repair, every effort should be made to abolish secondary tricuspid insufficiency by medical means before surgery.

The series has been limited to patients without aortic valve deformity. It is to be anticipated that greater familiarity will result in ability to repair also a stenotic aortic valve. Significant aortic regurgitation, a difficult problem in repair itself, poses a complicating factor in tricuspid and mitral open surgery which has not yet been accepted in this series. Without the use of cardiac arrest the constant regurgitation from the perfusion flow would necessitate intermittent occlusion of the aorta and seriously interfere with repair. Potassium arrest in hearts with aortic valve insufficiency is extremely dangerous because of the left ventricular distention which occurs between the time that coronary perfusion is restarted by removal of the aortic clamp and the onset of forceful ventricular contractions.

A further deterrent to this form of mitral-tricuspid surgery is the presence of severe pulmonary vascular changes secondary to the long-standing heart disease. This is not a strange contraindication to surgery, having long been an important factor in selection of patients for closed mitral commissurotomy.

Summary

A group of eight patients having primary mitral valvular deformity and intractable secondary tricuspid insufficiency were subjected to simultaneous operation on both valves.

Repair was done under total cardiopulmonary bypass by way of the lateral wall of the right atrium and the interatrial septum. Plication of the annulus of the tricuspid valve was done in each case. Either direct-vision commissurotomy or annulus plication was done on the mitral valve.

Two operative deaths and two late surgical deaths occurred in this series of poor-risk patients. Four very favorable results were obtained in the survivors, whose preoperative state was comparable to that of the patients who did not survive.

The advantages and disadvantages of potassium cardiac arrest as used in this series are discussed. High-flow, atraumatic perfusion through the use of a vertical cylinder bubble-diffusion oxygenator is discussed.

25 E. Washington St. (2).

REFERENCES

1. Julian, O. C.; Dye, W. S., and Grove, W. J.: Selection of Patients for Mitral Commissurotomy in Relation to Clinical Results, A. M. A. Arch. Surg. 69:273-281, 1954.

2. Effler, D. B.; Groves, L. K.; Martinez, W. V., and Kolff, W. J.: Open-Heart Surgery for Mitral Insufficiency, J. Thoracic Surg. 36:665-676, 1958.

3. Julian, O. C.; Lopez-Belio, M.; Dye, W. S.; Javid, H., and Grove, W. J.: The Median Sternal Incision in Intracardiac Surgery with Extracorporeal Circulation: A General Evaluation of Its Use in Heart Surgery, Surgery 42:753-761, 1957.

4. Kay, E. B.; Nogueira, C.; Head, L. R.; Coenen, J. P., and Zimmerman, H. A.: Surgical Treatment of Mitral Insufficiency, J. Thoracic Surg. 36:677-696, 1958.

5. Lillihei, C. W.: Discussion in Cardiovascular Postgraduate Course, 44th Clinical Congress, American College of Surgeons, 1958.

DISCUSSION

DR. EGBERT HOWARD FELL, Chicago: I enjoyed Dr. Julian's paper. This is a bold procedure, and Dr. Julian is a courageous person. His experiences are well worth listening to and extremely profitable. We have had a considerable number of cases (as all of you have) of tricuspid insufficiency, the essential hemodynamic pathology being mitral stenosis. They have responded well to commissurotomy. I am not sure that I could subject these patients to open heart surgery at the present time. The usual surgical procedure, mitral commissurotomy, I believe is here to stay except in complicated cases. Perhaps a severe tricuspid insufficiency is one that should be subjected to open heart surgery. Time will tell whether the additional load of open heart surgery is worth the risk taken, considering the excellent results obtained with the closed method of valvuloplasty.

DR. JOHN KIRKLIN, Rochester, Minn.: I appreciate the opportunity to comment very briefly on Dr. Julian's paper. Certainly all of us, I am sure, have had the experience of seeing patients with either mitral stenosis or mitral insufficiency develop secondary tricuspid insufficiency. They are indeed in the advanced stages of their disease, and it is my personal opinion that a mortality of 50% in this group in the present stage of our knowledge is not surprising. Indeed, I think one has reason to compliment Dr. Julian on having a 50% survival rate in this particular group of patients. I agree that the closed operation for mitral stenosis has stood the test of time very well; but in my own hands, at least, there are many times at the end of the operation when I feel that perhaps we could have done better had we had an open approach to the valve. I must therefore confess that I am in sympathy with Dr. Julian's tenet that in certain patients with mitral stenosis an open operation will prove to be advisable. I must also confess that I subscribe completely to his thesis that in these patients with severe tricuspid insufficiency this indication exists.

DR. ORMAND C. JULIAN, Chicago: At the moment, at least, we should not approach the problem of mitral surgery by open procedures in 100% of cases, although the future will almost certainly bring this about. We can't do it because there would not be time, and at least in Chicago there would not be the supply to accomplish this.

I should like to amplify one aspect of this series. The mortality was 50%. We approached the problem with a good deal of trepidation in the first place, but had good results to begin with. Of course, we would have discontinued it immediately if we had had the bad cases at the onset. However, actually what happened was that six patients survived the procedure and showed improved cardiac function. Two died at the time of surgery. The two late deaths were both, I am embarrassed to say, partly due to infection, although one patient had severe liver disease as a serious factor as well. So actually, even in poor-risk patients, I am sure the mortality will not be 50%.

Reoperation for Disruption of Repair of Interventricular Septal Defect

Utilization of Extracorporeal Circulation

JOHN C. CALLAGHAN, M.D.; JOSEPH DVORKIN, M.D., and DONALD BUCHANAN, M.D.,
Edmonton, Alta., Canada

In the early experience of any cardiovascular surgical unit utilizing total cardiopulmonary bypass for the repair of complex defects within the heart, there are undoubtedly certain defects incompletely closed. With the increasing experience of the operator, the number of these cases will decrease. However, with the great number of workers repairing these defects, incomplete closure will most likely continue to be a problem for some time to come. It is just such a problem that has stimulated this report.

When the realization that the operative procedure has been a complete failure, usually consisting of the return of hyperdynamic heart action, a thrill, and systolic murmur after the repair of a ventricular defect, certain aspects must be considered. The first of these is, of course, the sincere appreciation that the child has not in any way been benefited by the surgical procedure, no matter how lengthy and exhausting it may have been to the surgical group. Therefore, reoperation is as much indicated as was the original operation.

Very few, if any, reports can be found in the literature concerning repeat operation for inadequate closure of defects. Gerbode,[1] in over 100 cases, reoperated three times, once at 10 days, once at 3 weeks, and once at 3 months, and agreed with the experience of definite technical ease in the earliest case. We have had two instances of reoperation in the first 90 cases in our series. The first of these is presented in detail to bring out the associated problems of management.

Report of a Case

A 10-year-old girl was known to have had a cardiac murmur since the age of 18 months. Two years before admission for surgery she complained of easy fatigability and minimal dyspnea on severe exercise. Cardiac catheterization on Nov. 2, 1956, in the cardiovascular unit, University of Alberta, demonstrated a shunt at the ventricular level, equal to 1.63 times the cardiac output. Right ventricular pressure was recorded at 58/10 mm. Hg. The diagnosis of an interventricular septal defect was supported by the presence of a systolic thrill and a murmur of Grade 3 intensity over the third left interspace and plethoric lung fields in the radiogram. On Nov. 27, 1957, utilizing the bubble-oxygenator of Lillehei and De Wall * and elective asystole with acetylcholine, the defect in the posterior portion of the upper part of the ventricular septum, measuring 1.5×0.5 cm., was repaired, using a polyvinyl formalinized (Ivalon) patch, as shown in Figure 1. The bypass lasted 22 minutes. After the repair the thrill and murmur disappeared until the following morning, at which time there was a return of hyperdynamic right ventricular activity, with a thrill and murmur. A complete breakdown of the repair was evident on physical examination, and recatheterization on the second postoperative day confirmed that a shunt equal to that present preoperatively had occurred. The right ventricular pressure was recorded at 67/12 mm. Hg. Reoperation was carried out, using an identical system of cardiopulmonary bypass. The patch was found to be attached to the lower margin of the defect, and the stitches had pulled out from the upper margin of the defect, as shown in Figure 1. The patch was removed and the repair effected with 13 interrupted sutures. The duration

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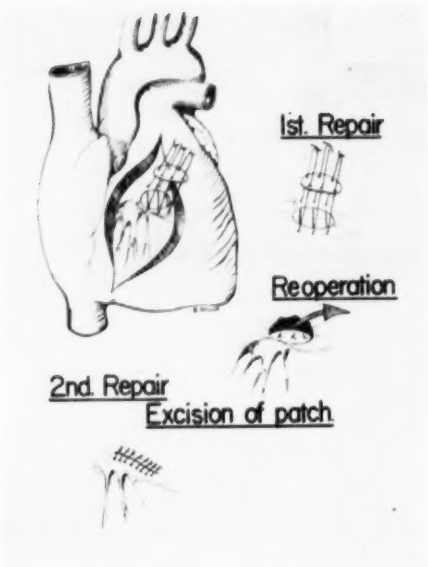

Fig. 1.—Interventricular septal defect in a girl 10 years of age.

of the bypass was 43 minutes in all. The postoperative period was uneventful. Total blood loss from the chest drains was 310 cc., as compared with a total chest drainage of 915 cc. following the first operation. She was discharged well on the 17th postoperative day.

At the follow-up examination, May, 1958, she was symptom free, and able to engage in competitive sports, and catheterization disclosed right ventricular pressure to be 30/6, with a trace of residual shunt, which was considered to be insignificant.

Comment

In the decision as to the correct time for reoperation, the problem of repeated massive transfusion was considered. It was decided that the earlier the operation, the safer so far as antibody formation was concerned.

The patient's known blood groups were A_1, MsNs, P_1, K+K+, Fy(a+), Le(a+b−).

Fourteen half-liter units of fresh blood were provided for each operation, half of the total volume being taken in silicone-coated glass bottles, each containing 18 mg. of heparin sodium in 30 ml. of isotonic saline. Thus the patient was exposed to the multiple antigens contained in 28 different donors' red cells, although all were, of course, compatible with regard to major group and Rh type.[3]

No irregular or immune antibodies were detected in either the patient's or the donor's serum prior to or following surgery, each serum having been screened separately against a panel of Group O trypsinized cells.

Cross matching was performed at 22 C in saline, at 37 C in saline and in 20% bovine albumin, and also by indirect Coombs testing. No incompatibilities were detected.

The venous samples were retested against a Group O panel derived from 16 different donors at intervals of 1, 6, and 14 weeks and 7 months following surgery. All tests, including indirect Coombs tests, have been consistently negative.

Abelson,[2] in a study of more than 30 Rh-negative volunteers, immunized by repeated injections of Rh-positive blood, found that anti-D (anti-ρ) appeared in the serums of more than 50% of the subjects, and a small number also became sensitized to anti-C serum. The first evidence of antibody formation appeared six to eight weeks after the initial dose of Rh-positive blood, but in some of the volunteers antibodies were not found until several years after the first injection of antigen, these experiments being conducted over a period of nine years.

In contrast, when blood is properly cross matched, sensitization is rarely detected. Thus, in following up blood samples from 27 other patients who had undergone open heart surgery, no immune antibody has been detected in any of their serums over a period of 18 months.[3]

Where multiple transfusions are being given to Kell-negative recipients, the modified capillary technique of Chown and Lewis can be used as a rapid method of excluding such K+ donors, provided always that one uses an anti-Kell serum of appropriate specificity.[4]

Excluding incompatibilities in the ABO, Rh, and Kell blood-group systems, it has been the experience of one of us (D. B.) that antibodies such as anti-Fy^a (anti-Duffy), anti-JK^a, etc., are rarely encountered, and in a region where over 30,000

blood transfusions are administered annually, these rarities have always involved persons who have been sensitized by transfusions given over a long period of time, and generally over many years. It would seem at first glance that massive transfusions of cross-matched blood might well result in sensitization. It is probable, however, that transfusions spaced over many weeks, months, or years are more dangerous in this regard; but follow-up studies of the serums of those undergoing open heart surgery will be of value in the future, provided always that sensitive techniques are used in the detection of irregular or immune antibodies.

As far as the technical ease was concerned, the second operation was completed without the aid of a scalpel, for finger dissection was quite satisfactory. In the postoperative period minimal discomfort was experienced by the patient, and the loss of blood from the pleural cavities was one-third the amount lost at the first operation.

Since the preparation of this report, a second patient suffering from a ventricular septal defect with aortic regurgitation due to prolapse of an aortic cusp has been reoperated upon on the 12th postoperative day, with a similar postoperative period following the second surgical intervention.

It is felt by this group that there may be an ideal time for repeat operation under total cardiopulmonary bypass, if needed, between the first and the third week after the initial surgery. The need for such repeat operative intervention will undoubtedly decrease with increase in experience of the operator.

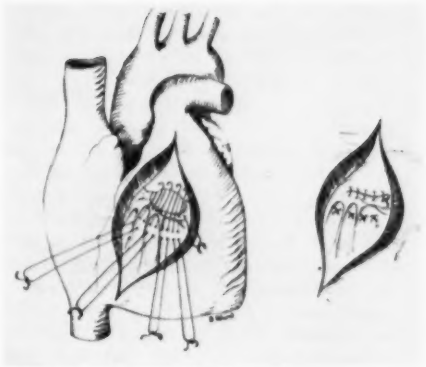

Fig. 2.—Kirklin repair of the defect.

At the present time we are using the repair described by Kirklin, as shown in Figure 2. This is undoubtedly a safe method of repair as far as the conductive mechanism is concerned.

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REFERENCES

1. Gerbode, F.: Personal communication, 1958.

2. Abelson, N. M.: Rh Sensitization of Volunteers: A Long-Term Study, read at the Sixth Congress of the International Society of Blood Transfusion, Boston, September, 1956.

3. Buchanan, D. I.; Afaganis, A., and Callaghan, J. C.: Massive Blood Transfusions and Extracorporeal Circulation, read at the Seventh Congress of the International Society of Blood Transfusion, Rome, September, 1958.

4. Lewis, M.: Personal Communication, 1958.

DISCUSSION

DR. TOM D. THROCKMORTON, Des Moines, Iowa: I always enjoy the papers at the Western Surgical Association meetings because I am always able to take home with me a pearl—and this paper is indeed my pearl for the day. As you may recall, Dr. Myerly and I spoke to this group several years ago, reporting a small series of patients who had been operated upon by means of an extracorporeal circulation. This group has now grown to more than 80 and contains 3 patients in whom the defect has recurred.

In our own experience there is only one operation that is more difficult to do than that on a recurrent intraventricular septal defect, and that is an operation on a recurrent intraventricular septal defect while standing up in a hammock. Our attempts at repair were at a much later date than has been suggested by the authors, and earlier operation sounds like an ideal way by which to approach an extraordinarily difficult problem. In our own group of patients we have had no recurrence of simple intraventricular septal defect; however, we have had three recurrences in the defect when associated with the tetralogy of Fallot. As we mentioned several years ago, there is something in the anatomy of these defects which I do not completely understand. The simple intraventricular septal defect has a tough fibrous edge, which will hold a stitch very well and may be sutured with every

anticipation of a permanently satisfactory result. However, in the tetralogy of Fallot, this tough fibrous edge is completely absent and the margin of the defect consists of soft cardiac musculature, through which a stitch can cut or slough with ease. It was interesting, however, in the three cases in which we reoperated, the original defect being a tetralogy of Fallot, that enough scarring at the margin of the defect resulted from the previous surgical repair to allow a simple closure without difficulty. The thought has crossed my mind that perhaps to reoperate on the defect of a tetralogy of Fallot within a week or two might well be like reoperating on a hernia which had recurred within a day or two of the first operation. Here is an instance in which the repair has already failed once, and a secondary repair would of necessity use tissues that were friable and torn. It is my thought that, in the case of a tetralogy, there might be something gained by withholding the operation until some scarring had taken place. However, the approach to the chambers of the heart and the recannulizing of the vessels required by extracorporeal circulation would obviously be greatly simplified by an early approach. As the authors have brought out, there is very little question as to the time when these defects recur. In our three cases the defect has recurred on the 5th to the 10th day after operation, and the recurrence has been quite obvious—one day the child is doing well and the next day he is in obvious cardiac failure. When we reoperate on our next recurrence, I am confident that the approach will be earlier, thanks to this report.

Dr. John Kirklin, Rochester, Minn.: It is a pleasure to have an opportunity to discuss Dr. Callaghan's paper for I think we have all been reluctant to state from a platform, as he did, that we have recurrences following ventricular septal defect repair. Certainly, it has been the experience of everyone in the field that just to take a patient with ventricular septal defect to the operating room, and then have him survive, is not necessarily the same as curing the patient. I think it is apparent, as time goes on, that in ventricular septal defect our problem revolves around the selection of cases for operation, the conduct of the operation and the perfusion, and then, most important, the securing of a complete repair and the avoidance of permanent heart block. I don't think any one of these is necessarily easy, and certainly I must confess that in our own hands the securing in every case of a complete and accurate and permanent repair has not always been successful. Therefore, we are all indebted to Dr. Callaghan for pointing out to us that it is possible in those cases where we have failed to again have a shot at the problem and to reoperate with a real hope of cure. It is our own belief, as Dr. Callaghan has so nicely emphasized, that in many, if not most, cases of ventricular septal defect it is possible to meet these goals of complete repair with the avoidance of heart block perhaps best by avoiding the employment of a prosthesis and by using direct suture. This has been true in the last year in our own experience, both in tetralogy and in the ordinary ventricular septal defect without pulmonary stenosis. However, even this probably does not always ensure complete and accurate and permanent repair. I think this contribution as to the ideal time at which to return in those occasional instances in which this is necessary is most important.

Dr. Ormand C. Julian, Chicago: Certainly the time to reoperate must be early. We have reoperated on a patient late and have had none of the ease of finger dissection that Dr. Callaghan described.

I should like to comment on the use of an Ivalon patch in interventricular septal defect. The defect that recurred, as shown by Dr. Callaghan, had been repaired by a method which, I believe, was described by Dr. Conrad Lam, in which the Ivalon patch is simply interposed on the sutures as they pass from one edge of the defect to the other. The Ivalon patch serves no real function when it is placed in this way, and I don't think the technique is used very often. I know Dr. Callaghan does not do it that way. The place for the sutures in an Ivalon patch, of course, is around the perimeter, where they can be tied loosely. Since the defect is not approximated edge for edge, the patch serves the purpose of preventing any tension on the sutures, and therefore they are less likely to disrupt and cause recurrence of a defect.

Dr. John C. Callaghan, Edmonton, Alta., Canada: All of us repairing these defects, I think, go through several stages. First, we are thrilled to have a living patient; then we have our first heart block. We probably do better in the repairing of the first couple of cases and then have a block, are a bit frightened for a while, and perhaps tend not to do a secure repair because of this. We are indebted to Dr. Lev for his anatomical study on the position of the conducting mechanism. We appreciate the guidance we have had by men like Dr. Kirklin, who have laid a pattern of a repair that is systematic.

Elongate Coarctation of the Aorta

FRANK MILLOY, M.D., and EGBERT H. FELL, M.D., Chicago

Four patients have undergone surgery for the treatment of elongate coarctation of the aorta during the past 10 years at either the Cook County or the Presbyterian Hospital of Chicago. We are presenting the salient features in these cases.

Report of Cases

CASE 1.—A 22-year-old Mexican woman was admitted to the hospital because of exertional dyspnea and precordial pain, which had been present since childhood. She also complained of headaches, dizziness, and numbness in her legs. Examination revealed blood pressures of 160/110 and 290/130 mm. Hg in the right and left arms, respectively. There were no pulses or blood pressure obtainable in the legs. The heart was enlarged to the left, and there were a systolic murmur and a thrill over the precordium. Aortography performed by retrograde technique through the femoral artery demonstrated an extremely long, irregular coarctation (Fig. 1). Exploration was done in the hope that a homograft might be used to bypass or replace the area of coarctation. This proved impossible because of the stony-hard consistency of the entire thoracic aorta, which seemed to be involved in a chronic inflammatory process. It was further noted that the coronary arteries, as well as other arteries of the body, were more sclerotic than might have been experted in a person of this age group. She has done fairly well in the four years since surgery and has had very little precordial pain.

CASE 2.—A 13-year-old white youth was admitted to the hospital because of palpitations, exertional dyspnea, and two-pillow orthopnea. His parents had been told that he had heart trouble early in his childhood. On examination, the pulse was found to be stronger at the right wrist than at the left and absent in the legs. Blood pressures were 176/90 and 142/110 mm. Hg in the right and left arms, respectively. None was obtainable in the legs. There was a systolic murmur over the precordium, heard best at the aortic area. Rib notching was present on the right. At surgery the coarctation was found in the usual location; however, the area of constriction was of an elongated hourglass contour, measuring about 4 cm. in length (Fig. 2). There was also stenosis of the left subclavian artery. This stenotic subclavian artery was divided and the aorta sufficiently mobilized that the central, most narrowed area of coarctation could be resected. Although the reestablished lumen of the aorta was not as large as that usually obtained following repair of coarctation, it was believed to be adequate.

The pathologic changes in the aortic wall were described as typical of those seen in the adult type of congenital coarctation, and there was no evidence of round-cell infiltrates or of a chronic inflammatory process.

Seven years after surgery the blood pressures are 155/90 mm. Hg in the right arm and 165/100 mm. Hg in the legs. The systolic pressure in the left arm is 30 mm. Hg less than in the right.

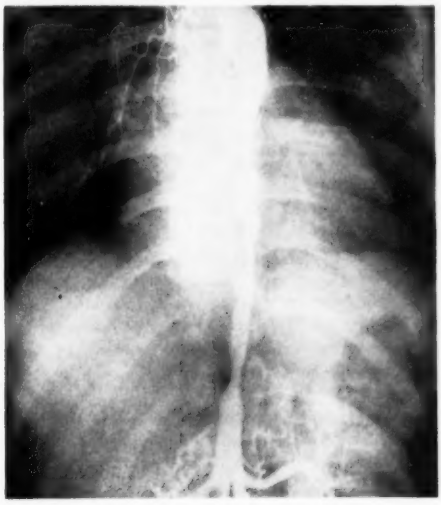
CASE 3.—An 18-year-old white youth was admitted to the hospital because of weakness of the legs after exercise, which he had noted as long

From the Presbyterian and Cook County Hospitals.

Read at the 66th Annual Meeting of the Western Surgical Assocation, Rochester, Minn., Nov. 21, 1958.

Aided by the grants from the Chicago Heart Association and the Otho S. A. Sprague Memorial Institute.

Fig. 1.—The aortogram illustrates the long, irregular coarctation seen in Case 1.



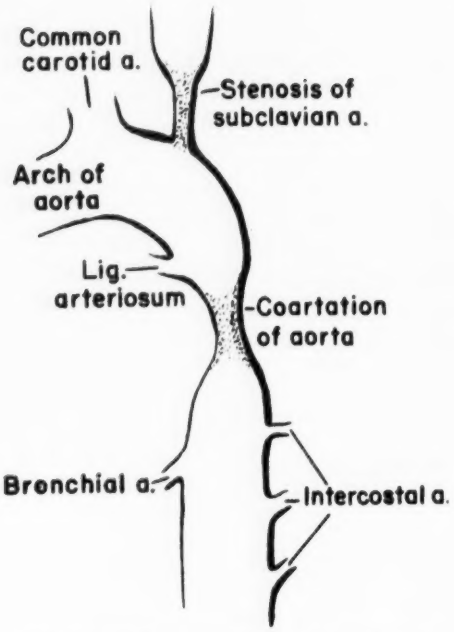
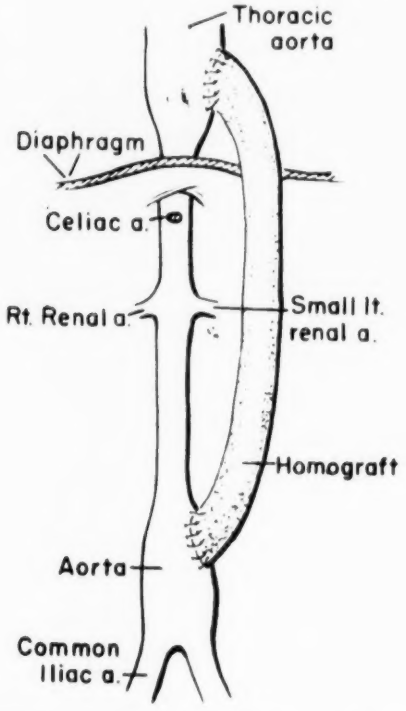


Fig. 2.—The diagrammatic sketch illustrates the 4-cm.-long coarctation and the stenosed left subclavian artery seen in Case 2.

as he could remember. He also complained of cramps in his feet, chest pain, and headaches, which had increased in severity over the past three years. He had been noted to have hypertension at the age of 13. Examination revealed the blood pressures to be 180/120 and 210/130 mm. Hg in the right and left arms, respectively. The brachial systolic pressure had been recorded to be as high as 280 mm. Hg. Pressures in the legs were 110/80 mm. Hg. The heart was enlarged to the left, and there was a systolic murmur at the xyphoid. Notching was present in the lower ribs. Direct aortic pressures were measured by means of a catheter introduced through the brachial artery, and the pressure was found to fall as the catheter passed down the aorta beyond the level of the 12th thoracic vertebra. Laboratory work-up, including excretory-dye studies, established the presence of normal renal function.

Through a thoracoabdominal incision, a coarctation was demonstrated, measuring 7 cm. and extending from 1 in. above the diaphragm to a level below that of the renal artery origins (Fig. 3). An aortic homograft bypass was inserted by means of two end-to-side anastomoses from just above the stenosed area to the abdominal aorta distal to the renal arteries.



Long Coartation of Thoracic & Abdominal Aorta

Fig. 3.—The drawing shows the elongate thoracoabdominal coarctation seen in Case 3 with the bypass homograft in place. The left renal artery was found to measure 2 mm. in diameter at the time of subsequent nephrectomy.

The patient did fairly well immediately after this procedure. Three months postoperatively, however, he was readmitted with a blood pressure of 260/140 in the arms and 280/140 in the legs. Renal function, as evaluated by Dr. Robert M. Kark at this time, revealed good concentration and dilution ability. The urine showed a trace of albumin. The retrograde pyelogram was normal. The maximal tubular excretion of *p*-aminohippuric acid was normal. Renal plasma flow was 554 cc/min. (predicted normal 675 cc/min.), and inulin clearance was 61.2 cc/min. (predicted normal 130 cc/min.). Differential ureteral catheterization revealed a urinary sodium content of 34 mEq/L. on the right and 13 mEq/L. on the left. The plasma sodium was 143 mEq/L.

Because of the mounting blood pressure, exploration was carried out through a left paramedian incision to determine whether there was any gross disturbance of the renal arterial blood supply. At

surgery the previously inserted graft was found to be patent and functioning. The kidneys, as well as the right renal artery, appeared grossly normal; however, there was no true left renal artery. Instead, a number of small vessels left the aorta to enter the left kidney. This kidney was removed, on the assumption that it was producing a Goldblatt effect.

Postoperatively the patient has done well. His last recorded blood pressure, two years after surgery, was found to be 170/95 and 200/100 mm. Hg in the upper and lower extremities, respectively.

CASE 4.—A 16-year-old white youth complained of easy fatigability of four years' duration. The onset was accompanied by a bout of fever and malaise, thought by his physician to be rheumatic fever. Over the past year he had developed a "murmur," and he had noted a buzzing noise in the right side of his neck.

Examination revealed pulses present in the arms and absent in the legs. Blood pressures were 160/120 and 140/100 mm. Hg in the right and left arms, respectively, and were unobtainable in the legs. Carotid pulsations were visible, and there was a bulging mass in the right supraclavicular area, over which a bruit could be heard. Rib notching was present.

At surgery a coarctation was found, measuring 10 cm. in length, distal to a large left subclavian artery. Above the coarctation the usually short segment of aorta between the left common carotid and the left subclavian artery was found to be elongated into a tortuous loop which extended high in the mediastinum, behind the left subclavian artery. The left subclavian was divided at its origin and the distal end oversewn. After excising the coarctation, it was possible to mobilize sufficiently the previously described loop of aorta so that its distal end could be brought down and an end-to-end anastomosis performed (Fig. 4).

Microscopic examination of the resected specimen showed thickening of the vessel layers, as seen in the congenital adult type of coarctation, with no suggestion of a chronic inflammatory process.

The patient made an uneventful recovery.

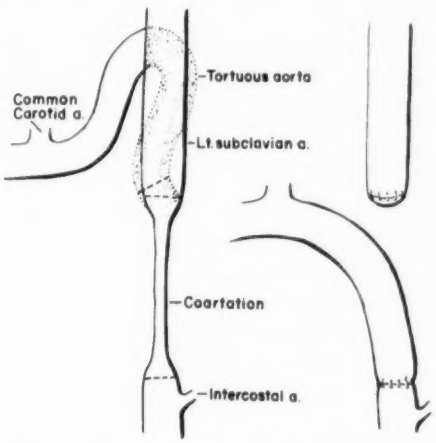


Fig. 4.—The diagrammatic sketch illustrates the 10-cm.-long coarctation and tortuous, anomalous loop of aortic arch which arose between the left common carotid and the left subclavian artery in Case 4. The inset at the right shows the repaired aorta, after excision of the coarctation, and the sutured left subclavian artery.

Comment

Elongate areas of stenosis or obliteration may occur at any level along the aorta. In a review of the literature, we have found 14 cases of elongate coarctation affecting the descending aorta in the region extending from the origin of the left subclavian artery to the origin of the renal arteries. The important features of these cases are summarized in the Table.

Elongate coarctations involving the aortic arch and the few reported cases of involvement of the abdominal aorta below the renal vessels[2,17] have not been included in this study. Several cases of low-lying thoracic coarctations, which were probably elongate,[4,7,21] have likewise been excluded because of insufficient information on the lengths of the lesions.

Characteristics of Elongate Coarctation.—It appears from the literature that this condition has no racial limitations. It has been reported in Negroes, Japanese, Argentinians, Jews, and among Western Europeans of various nationalities.

A review of the cases summarized in the Table, however, reveals several differences between the usually encountered adult type of short coarctation of congenital etiology and the elongate type of coarctation, which evidently may be of congenital or acquired etiology.

The sex incidence of the two entities is definitely reversed. The commonly encountered adult type occurs more frequently in males, in a ratio of 2:1 or 3:1, while the rare elongate type is reported more commonly in females.

Elongate Coarctations Reported in Literature Exclusive of Those Involving the Aortic Arch or Those Found Below the Renal Arteries with Four Additional Cases

Case No.	Senior Author, Year	Age	Sex	Maximum Blood Pressure, Mm. Hg	Description of Coarctation	Other Information
1	Schlesenger [20] 1835	15	F		2 in. long, just above diaphragm; would admit fine probe	Severe attacks of dyspnea, with convulsions, for 2 yr.
2	Hasler [10] 1911	49	M		2.5 cm. long, 3 cm. above diaphragm with obliterated lumen	Asymptomatic
3	Hickl [11] 1931	38	F		6 cm. long, 3 cm. above diaphragm; aortic wall thickened; perivascular round-cell infiltrations but no Aschoff bodies found	Two-yr. history of rheumatic-type infection; author thought lesion to be of inflammatory origin
4	Olim [14] 1949	20	F	200/140	Rather long stenotic area 5 cm. above diaphragm; aortic wall rigid and pipe-like with no elasticity; intima and media separated when aorta cut across	Negro; 11-yr. history of headaches
5	Bahnson [2] 1949	17	F	180/90	4 cm. long, two interspaces below the isthmus; wall of aorta thickened and indurated	Headaches 15 mo. and hypertension 8 mo. previously; had been active and in good health
6	Kondo [15] 1950	12	F	40/?	Marked coarctation between superior mesenteric and renal arteries, extending to bifurcation	Japanese. Weakness and lassitude for 3 yr.; hypoplastic and anomalous subclavian arteries (other congenital anomalies)
7	Freeman [6] 1950	14	F	225/125	Coarctation from T-11 to L-1, with marked constriction	X-ray diagnosis (aortogram) in patient with multiple congenital defects
8	Beattie [3] 1951	19	F	180/110	6 cm. coarctation, extending from T-9 downward	Known hypertension for 3 yr.
9	Jönsson [13] 1951	15	F		3 cm. long in midthoracic aorta	X-ray diagnosis
10	Glenn [9] 1952	19	F	220/175	10 cm. long from T-10 to celiac axis; lumen 5 mm.; ring of neurofibrous tissue about aorta at proximal portion of coarctation	Jew. Neurofibromatosis and multiple congenital anomalies; patient had hypertension for 10 yr.
11	Deterling [5] 1953	26	F	200/85	9 cm. long, 6 cm. above diaphragm with obliterated subclavian; pleura thickened and adherent; perivascular round-cell infiltrations	Puerto Rican. Symptoms referable to cardiovascular system for several months; resection with graft
12	Albanese [1] 1953	12	F	240/	5 cm. long from diaphragm to renal arteries; lumen seemed obliterated; aorta narrowed above coarctation	Argentinian. Had developed scarlet fever and heart murmur 5 yr. previously; pt. died of hypertensive encephalopathy after insertion of bypass homograft
13	Hulting [12] 1955	10	F	180/90	1.5 cm. constriction at diaphragm with conical narrowing of aorta at either end	X-ray diagnosis
14	Konar [16] 1955	13	F	250/140	8 cm. long from midthoracic aorta to diaphragm; vessel hard, thick, and adherent to pleura; perivascular roundcell infiltration present	From India. History of shifting joint pains and fever for 2 yr.
Case 1		22	F	200/130	Extremely long, irregular coarctation from just below isthmus to diaphragm; aortic wall thickened and pipe-like; pleura adherent	Mexican. Symptoms since childhood; not amenable to surgery; thought to be of acquired etiology
Case 2		13	M	170/90	4 cm. at isthmus; stenotic subclavian	Thought to be congenital in etiology
Case 3		18	M	210/130	7 cm. from 1 in. above diaphragm to below renal-artery origins	Aortic homograft bypass; later required nephrectomy because of Goldblatt hypertension; thought to be of congenital etiology
Case 4		16	M	160/120	10 cm. at and below the isthmus; anomalous tortuosity of aortic arch	Thought to be of congenital etiology; excision and anastomosis

From the standpoint of the gross pathology, the adult type of coarctation is a sharp constriction of the aorta, in which a shelf-like diaphragm projects into the lumen of the vessel. In the elongate type the normal aorta tapers in hourglass fashion at either end of a stenosed or obliterated length of aorta, which usually measures several centimeters.

The location of the elongate coarctations at the lower levels along the aorta is another commonly noted difference between these two conditions. Although the sharp constricting type of coarctation has been reported at lower levels on the aorta,[13,19] and elongate coarctation may occur at the isthmus (as in our second and fourth cases), the usual location of elongate coarctation is below the aortic isthmus, whereas the vast majority of typical congenital coarctations occur at the aortic isthmus.

In addition, in the elongate type, the aortic wall, both at the actual area of constriction and for some distance above and below this area, is frequently found to be thickened and to have lost its elasticity. When the vessel has been divided at surgery and suturing attempted, the intimal and medial layers of the aortic wall have been observed to split apart with ease.[18] Furthermore, the pleura overlying the area of coarctation may be thickened and more adherent to the vessel than is normally found.

This evidence of chronic inflammation about the area of coarctation, together with the presence of perivascular round-cell infiltrations, which have been described on microscopic examination of these vessels, has led some observers to term these lesions "acquired coarctations." This theory of inflammatory origin of elongate coarctations is further strengthened by the fact that several of the victims have given a definite history of rheumatic symptoms.

On the other hand, proof of rheumatic infection has not been positively established in any of these cases: furthermore, the occurrence of associated congenital anomalies has convinced other observers that the etiology of their cases was congenital.

Possible Relationship to Other Types of Arteritis.—If, as some suspect, there is an inflammatory etiology for some of these coarctations, it may be an arteritis similar to that which has been noted to affect the great vessels branching from the aortic arch and which is thought to be the cause of a condition known as "pulseless disease." Frövig[8] describes a case of this disease which he encountered and lists 10 additional cases from the literature. An interesting fact noted in his report was that all cases occurred in women between the ages of 20 and 40. The pathologic changes, which were those of a nonspecific, chronic arteritis, were noted in various cases of this disease to occur in all portions of the aorta, as well as in the great vessels leaving the arch. Frövig concluded that the condition belongs to the group of diseases thought to be of "allergic-hypergic" origin, a group which, among others, includes endarteritis obliterans, rheumatic disease, periarteritis nodosa, and giant-cell arteritis.

Comparison of Present Cases with Previous Cases.—In a comparison of the four cases presented here with those previously reported in the literature, it would seem that Case 1 was of the type generally thought to be of acquired etiology and that the other three cases were of congenital etiology. This presentation is not an attempt to give criteria for determining the etiology of these lesions, however, and this is only an opinion reached on the basis of gross observations at surgery and microscopic examination of the resected specimens.

The unusual deformity of the aortic arch noted in Case 4 seems best explained on the basis of a congenital anomaly. Because of this fact, and because of the absence of any evidence of a chronic inflammatory process grossly or microscopically, this coarctation was thought to have been of congenital etiology. This was in spite of the history of rheumatic infection.

It was of interest to note the great similarity between Case 3 and the case reported by Albanese.[1] The homograft placed in these two patients with abdominal coarctations evidently caused sufficient alteration in the renal hemodynamics of the ischemic left kidneys to precipitate crises through the mechanism of the Goldblatt effect. Fortunately, the hypertension was not so acute in this case and was amenable to surgical correction.

Summary

Four cases of elongate coarctation are presented involving the aorta in the region between the arch and the renal vessels. A review of the literature revealed 14 similar reports, although some probable cases were eliminated because of a lack of specific information concerning the lengths of the coarctations. In addition to the difference in the length of the constricted area in the two types of coarctation, there are other distinguishing features. The sex incidence is reversed, and, in contrast to the usual short coarctation, elongate coarctation occurs most frequently in females. Furthermore, it is usually located below the isthmus and may involve the abdominal aorta, whereas the typical sharply constricting adult coarctation of congenital origin occurs at the isthmus in the vast majority of cases.

There is frequently evidence of an inflammatory process involved in elongate coarctation, characterized by induration and thickening of the aortic wall and overlying pleura and microscopic findings of perivascular round-cell infiltrations. These findings suggestive of chronic inflammation have led some observers to believe that there might be an acquired etiology for this condition. Since the great vessels leaving the aortic arch may be involved by a nonspecific chronic arteritis, it is conceivable that a similar process may involve the aorta itself and that there may, in fact, be an inflammatory element in the etiology of some of these constrictions.

From the observations made at surgery in these four cases as compared with the previously described cases in the literature, it would seem that the first case presented could have been of acquired etiology and that the other three cases were probably of congenital origin.

The treatment of this condition, when possible, consists of an aortic prosthetic replacement or bypass.

122 S. Michigan Ave. (3) (Dr. Fell).

REFERENCES

1. Albanese, A. R., and Lazzarini, A. A.: Coarctation of the Abdominal Aorta—Graft of Preserved Aorta, Angiology 4:429-435, 1953.

2. Balnson, H. T.; Cooley, R. N., and Sloan, R. D.: Coarctation of the Aorta at Unusual Sites: Report of 2 Cases with Angiocardiographic and Operative Findings, Am. Heart J. 38:905-913, 1949.

3. Beattie, E. J., Jr.; Cooke, F. N.; Paul, J. S., and Orbison, J. A.: Coarctation of the Aorta at the Level of the Diaphragm Treated Successfully with a Preserved Human Blood Vessel Graft, J. Thoracic Surg. 21:506-512, 1951.

4. Brock, R. C., and Graham, A. J. P.: Resection of Combined Aneurysm and Coarctation of the Aorta with Insertion of a Homograft, Guy's Hosp. Rep. 101:207-215, 1952.

5. Deterling, R. A., Jr.: Resection of an Acquired Coarctation of the Low Thoracic Aorta and Replacement with a Preserved Vessel Graft, J. Thoracic Surg. 26:290-299, 1953.

6. Freeman, N. E.; Miller, E. R.; Stephens, H. B., and Olney, M. B.: Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions: II. Coarctation of the Aorta, Ann. Int. Med. 32:827-841, 1950.

7. Froment, R.; Gallavardin, L., and Noel, G.: Des formes basses, sous-isthmiques, de sténoses congénitales de l'aorte, á propos de trois cas personnels, Arch. mal. cœur 45:496-502, 1952.

8. Frövig, A. G., and Löken, A. C.: The Syndrome of Obliteration of the Arterial Branches of the Aortic Arch, Due to Arteritis: Post-Mortem Angiographic and Pathological Study, Acta psychiat. et neurol. scandinav. 26:313-337, 1951.

9. Glenn, F.; Keefer, E. B. C.; Speer, D. S., and Dotter, C. T.: Coarctation of the Lower Thoracic and Abdominal Aorta Immediately Proximal to the Celiac Axis, Surg. Gynec. & Obst. 94: 561-569, 1952.

10. Hasler, L. H.: Über einen Fall von Verschluss der Aorta an Ungewohnter Stelle, Borna-Leipzig, R. Noske, 1911.

11. Hickl, W.: Über zylindrische Aortenverengerung im absteigenden Brustteil infolge von Mesoaortitis, Frankfurt. Ztschr. Path. 41:176-183, 1931.

12. Hulting, B., and Vendsalu, A.: Coarctation of the Aorta in Unusual Sites, Acta radiol. 43: 453-458, 1955.

13. Inmon, T. W., and Pollock, B. E.: Coarctation of the Abdominal Aorta, Am. Heart J. 52: 314-320, 1956.

14. Jönsson, G.; Brodén, B., and Karnell, J.: Thoracic Aortography, Acta radiol., Supp. 89, 1951.

15. Kondo, B.; Winsor, T.; Raulston, B. O., and Kuroiwa, D.: Congenital Coarctation of the Abdominal Aorta, a Theoretically Reversible Type of Cardiac Disease, Am. Heart J. 39:306-313, 1950.

16. Konar, N. R.; Chaudhury, D. C. R., and Basu, A. K.: A Case of Coarctation of the Aorta at an Unusual Site, Am. Heart J. 49:275-280, 1955.

17. Maycock, W. d'A.: Congenital Stenosis of the Abdominal Aorta, Am. Heart J. 13:633-646, 1937.

18. Olim, C. B.: Coarctation of the Aorta at the Level of the Diaphragm: Case Report, Ann. Surg. 130:1091-1097, 1949.

19. Schleckat, O.: Angeborene ringförmige Stenose der Aorta Descendens in Zwerchfellhöhe, Ztschr. Kreislaufforsch. 25:417-419, 1933.

20. Schlesinger, H.: Merkwürdige Verschliessung der Aorta, Wchnschr. ges. Heilk. 31:480-496, 1835.

21. Steele, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta: Report of 3 Cases, J. Clin. Invest. 20:473-480, 1941.

DISCUSSION

DR. EGBERT H. FELL, Chicago: Each of the four cases presented this morning is a separate problem and could have made a 10-minute presentation. The first patient, who appeared to have a coarctation of the aorta, has generalized sclerotic disease which presented the picture of a coarctation. When we first saw this young woman, her main complaint was that of severe angina, to the point where she was receiving a good deal of narcotic medication and oxygen. An exploration of the chest in another city four years prior to admission revealed "no aorta." Our examination showed marked pulsations in the left of her neck and none on the right side. A systolic blood pressure of over 200 mg. Hg was obtained in the left arm, and it was difficult to obtain any pressure in the right arm and lower extremities. In our cardiovascular physiology laboratory, a very interesting aortogram was made, showing the marked irregular narrowing deformity of the entire thoracic aorta. The possible etiology is intriguing. It may be on a metabolic basis; it may be hereditary, or it may be a type of "pulseless disease." Exploration revealed a very sclerotic aortic arch, and a thoracic aorta with irregular areas of thickening of the wall and narrowing of its lumen. The coronary vessels showed similar pathology; no gross myocardial involvement was seen.

Another interesting patient was the 16-year-old boy with the tortuous aortic arch (between the left common carotid artery and the left subclavian artery) associated with a stenosis of the aorta, 10 cm. long, distal to the subclavian artery. We have had no similar case. At first we could not find the aortic arch, but later in the dissection we found this tortuous aorta in the apex of the left chest, looped behind the subclavian artery. The Lord was very kind to this patient. We used this tortuous, long loop by freeing it from the subclavian artery and bringing it distal to the recurrent laryngeal nerve, thus bridging the 10 cm. defect.

DR. JOHN T. REYNOLDS, Chicago: What happened to the patient afterward? Did she develop gangrene of the legs?

DR. EGBERT H. FELL, Chicago: Permission for autopsy was obtained from her husband directly after the exploration. We did not expect her to leave the hospital. That was three and a half years ago. She came to the hospital six months ago, really very comfortable, with considerable relief of her angina, and she was taking care of her home.

Prevention of Thrombus Formation in Small-Artery Anastomoses

HAROLD S. ENGLER, M.D.; PHILLIP E. CHRISTOPHER, M.D.; H. GRADY WILLIAMS; ROBERT S. SPEARS, and WILLIAM H. MORETZ, M.D., Augusta, Ga.

The present vigorous activity in vascular surgery is chiefly focused upon the larger vessels of the body, such as the aorta and iliac and femoral arteries. Remarkable progress has been made, and successful replacements, shuntings, and endarterectomies are commonplace in these larger vessels. Much less attention has been given to the smaller arteries, where the need is perhaps even greater. An exception is the coronary artery, which has received, and is receiving, much study. The problems involved in securing successful anastomoses in large arteries are no doubt similar to those encountered in small-vessel anastomoses, but in the smaller vessels there is a far greater tendency toward occlusion of the anastomotic site by thrombosis. Because of this tendency of small-vessel anastomoses to occlude, the techniques which have been used so successfully in large vessels often fail in small arteries.

Reports have varied considerably in the degree of success achieved when small arteries have been anastomosed, but most investigators agree that a high incidence of failure occurs when the outside diameter of the arteries is 4 mm. or less.

Our purpose in this study was to modify to some extent certain factors which probably contribute to the development of thrombosis at the site of anastomosis in an effort to decrease the incidence of thrombosis. These factors would be altered so far as possible, one at a time, in order to determine their relative importance. The attempt would be made to modify the current of injury, normally present at a site of trauma, by creating a highly negative electrostatic field. Stasis would be diminished by (1) performing the anastomosis in such a way that the usual constriction would be eliminated and (2) creating an arteriovenous (A-V) fistula distal to the end-to-end anastomosis to increase the rate of blood flow. Extension and enlargement of the minute thrombi present in the suture line and needle holes would be combated by (1) fibrinolysin and (2) heparin.

Materials and Methods

Dogs weighing from 6-12 kg. were selected so that the external diameter of the femoral arteries would be 4 mm. or less, with an average of about 3 mm. The outside diameter of the vessel was measured immediately upon encountering the normally distended vessel prior to any dissection which might lead to vasoconstriction. Operations were performed under pentobarbital (Nembutal) anesthesia, using aseptic technique. The segment of artery to be used was carefully stripped of adventitia. Care was taken to keep the vessels moist. The Carrel suture technique was used, placing three triangulating guide sutures and a continuous whipstitch between each two of the guide sutures. Number 000000 arterial silk was used throughout. The sutures were placed through the vessel wall as near the cut edge as possible. Bleeding, encountered to some extent in almost every anastomosis, was usually controlled by very lightly applied finger pressure. In a few instances additional sutures were used in an effort to stop bleeding, but usually this led to more bleeding. As a routine, animals were killed on the seventh postoperative day, being anesthetized for exposure and examina-

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From the Department of Surgery, Medical College of Georgia, and the Eugene Talmadge Memorial Hospital.

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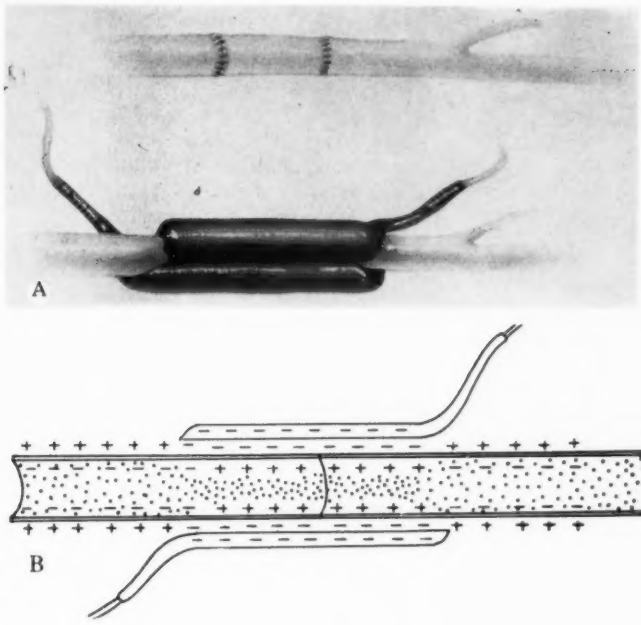


Fig. 1. — (*A*) The homograft has been sutured into position (above). The arrangement of the insulated (plastic-coated) electrodes is shown below completely covering the homograft and adjacent ends of femoral artery.

(*B*) The normal potential difference between vessel adventitia and intima is illustrated diagrammatically at each end, with the reversal of this potential difference near the point of transection depicted centrally. The streaming of the formed elements of the blood away from the vessel wall beneath the electrodes represents the desired effect of the field produced by the high negative charge on the electrodes.

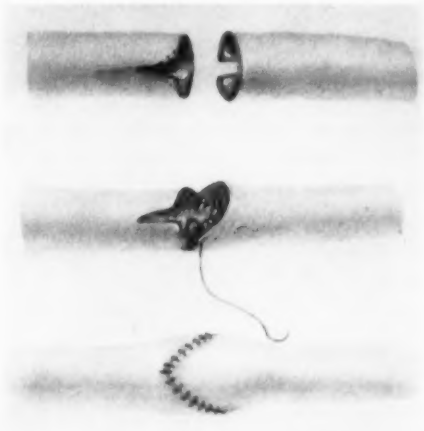
tion of the anastomotic site while still alive. Animals were then killed, and the anastomotic area excised, opened, and examined carefully for thrombus. It was felt that observation for seven days would include almost all thrombotic occlusions, since most of these are thought to occur within the first two days.[1]

Group I: *Electrostatic Field.*—On each side a 1 cm. long, alcohol-preserved homograft of the same size as the host artery was anastomosed into a 1 cm. defect. A 5-6 cm. long, hemicylindrical, and insulated electrode was placed on each side of the vessel, thus completely surrounding the homograft, the anastomoses, and the adjacent normal artery bilaterally (Fig. 1). Two hundred fifty volts was delivered from the negative pole of a D. C. voltage regulator to the electrodes on one artery only, the opposite artery being the control. The electrodes, with the induced electrostatic field on one side, were left in place for six hours, after which they were removed and the wounds closed. In a control group of four dogs, similar anastomoses and placement of electrodes were carried out, but no voltage was applied to either side.

Group II: *Modified Anastomosis.*—In this series a standard anastomosis was performed on one side, and a modified anastomosis similar to that described by Linton[2] was performed on the other. The modification consisted of making a longitudinal incision one-half the vessel circumference in length on opposite sides of the ends to be anastomosed, as shown in Figure 2. This, in effect, accomplishes the same thing as closing transversely a longitudinal incision in the bowel, enlarging and angulating the anastomosis.

Group III: *Arteriovenous Fistula Distal to End-to-End Anastomosis.*—Standard end-to-end anastomoses were made bilaterally. One centimeter

Fig. 2.—Modified end-to-end anastomoses (Linton). The cleanly divided ends of the artery were incised longitudinally on opposite sides for a distance of about one-half the circumference of the artery. The sharp corners are rounded before suturing with a running whip stitch.



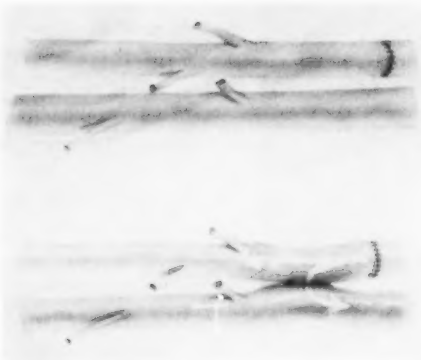


Fig. 3.—The relationship of the end-to-end arterial anastomoses and the distally placed arteriovenous fistula is illustrated.

distal to the anastomosis on the right side a 1 cm. long anastomosis was made between the femoral artery and vein using a continuous suture posteriorly and another anteriorly (Fig. 3). Similar lengths of vessels were freed on the left side, even though no fistula was made there, in order to make it a more comparable control. The anastomosis done first alternated between the left (control) side and the right (end-to-end, A-V fistula) side. Occluding arterial clamps were applied proximally and distally just before performing the anastomoses, and in each instance the occluding clamps were removed from the two sides simultaneously. In a few instances aortograms were made before killing the animals.

Group IV: *Use of Intravenous Fibrinolysin.*—Standard end-to-end anastomoses were made in the femoral artery bilaterally. Several different schedules of fibrinolysin administration were tried. Five animals received 10,000 units in 250 cc. of isotonic saline as a slow drip during the operation. Thirteen animals received 10,000 units in 10 cc. of isotonic saline immediately before surgery, and again on the second postoperative day. Three animals received 20,000 units in 10 cc. of isotonic saline immediately before operation only. This enzyme required activation with 5,000 units of streptokinase per 10,000 units. In a control group, consisting of six dogs (12 femoral arteries), an identical technique was used but no fibrinolysin was given.

Group V: *Heparinization.*—Standard anastomoses were made bilaterally in the femoral arteries. In each dog prior to or just following the completion of the anastomoses, both aqueous heparin and heparin in oil were given in varying amounts and schedules, as indicated in Table 5.

Results

Of the 13 dogs in the *electrostatic field group*, 11 were considered acceptable for study, 2 of the animals being anesthetic deaths during the six-hour period of electrostatic-field application. The animals varied in weight from 5 to 10.5 kg., the average weight being 7.5 kg. The effects of the electrostatic field on the incidence of thrombosis are shown in Table 1.

Table 1.—*Effect of Electrostatic Field on Thrombosis Using Homografts*
Average Diameter of Arterities—3.0 mm. (2.5-4 mm.)

No. Dogs	"Field" Side *	Contro Side
A. Electrodes Applied About Homografts Bilaterally with "Field" Created on One Side		
8	T	T
1	P	P
1	T	P
1	P	T
Total 11	9 T	9 T
	2 P	2 P
B. Homografts Bilaterally But Without "Fields" or Electrodes		
4	7 T	
	1 P	

* T = thrombosed; P = patent.

The average weight of the 13 animals in the *modified end-to-end anastomosis study* was 12 kg., the largest weighing 13 kg. and the smallest weighing 8.5 kg. The incidence of thrombosis is given in Table 2. Seven dogs were killed eight days after operation; three were killed about one month after operation, and three were killed about five

Table 2.—*Effect of Modified End-to-End Anastomosis on Thrombosis*
Average Diameter of Arteries 3.0 mm. (2.7-3.5 mm.)

No. Dogs	Modified Anastomosis *	Standard Anastomosis
3	T	T
7	P	P
1	P	T
2	T	P
Total 13	5 T	4 T
	8 P	9 P

* T = thrombosed; P = patent.

months after operation. It was of interest that of the six dogs not killed early, the incidence of thrombosis was less than in those killed on the eighth day, only one anastomosis of the control and one of the modified group being thrombosed.

The 20 dogs used for the *A-V fistula* study averaged 8.4 kg. in weight, and the femoral arteries averaged less than 3.0 mm. in outside diameter, with a range of 2.25 to 3.5 mm. (15 dogs had arteries of 3.0 mm. or less in outside diameter). The incidence of thrombosis at the end-to-end anastomosis was again disappointingly high, as shown in Table 3. In each instance in which the

TABLE 3.—*Effect of Increased Blood Flow on Thrombosis at Anastomosis*
(Distal A-V Fistula)

No. Dogs	Standard Anastomosis with A-V Fistula	Standard Anastomosis
7	T	T
2	P	P
5	P	T
6	T	P
Total 20	13 T 7 P	12 T 8 P

* T = thrombosed; P = patent.

end-to-end anastomosis on the A-V fistula side was thrombosed, the A-V fistula also was thrombosed.

The effect of *fibrinolysin* was observed in 21 dogs (42 femoral arteries). These were small dogs, weighing between 6.2 and 13.2 kg., whose femoral arteries averaged 3.0 mm. in outside diameter (ranging from 2.5 to 4.0 mm.). The total number of patent anastomoses was 14, and the number thrombosed was 28. The possible difference in effectiveness of the various dosage schedules can be seen in Table 4. In a separate control series for this group, 12 arteries of similar size were anastomosed, 5 remaining patent and 7 becoming thrombosed.

The *effectiveness of heparin* on thrombosis was apparent even in these incomplete studies. These animals weighed between 10.7 and 13.8 kg., with femoral arteries ranging

TABLE 4.—*Effect of Fibrinolysin on Thrombosis*

	No. of Arterial Anastomoses *	No. Patent	No. Thrombosed
Fibrinolysin			
10,000 units by slow drip during operation	10	1	9
10,000 units immed. preop. and on 2d p. o. day	26	10	16
20,000 units immed. preop.	6	3	3
Totals	42	14 (33%)	28 (67%)
Controls (6 comparable dogs without fibrinolysin)	12	5 (42%)	7 (58%)

* Total of 21 dogs with average weight of 9 kg. (6.2-13.5 kg.) and average outside diameter of arteries of 3.2 mm. (2.5-4.0 mm.)

between 2.5 and 3.5 mm. in outside diameter, (average outside diameter, 3.1 mm.). The proper dosage was not ascertained, the larger doses preventing thrombosis but also causing massive and fatal hemorrhage and the smaller doses leading to relatively little hemorrhage but being less effective in preventing intravascular thrombosis. If we are allowed to exclude the animal in which massive infection occurred, the incidence of thrombosis was significantly reduced even with small amounts of heparin (Table 5).

Comment

There is general agreement that anastomoses in small arteries (4.0 mm. or less in

TABLE 5.—*Effect of Heparin on Thrombosis at Anastomoses*
(Preliminary Experiments)

	No. of Anastomoses	Period of Observation, Days	State of Anastomoses
Group I: Large dosage 1 to 3 mg/kg. I. V. (aqueous) and 100-200 mg. I. M. (Depo); given prior to anastomosis	10	1-3	All patent
Group II: Small dosage * 0.3 mg/kg. I. V. (aqueous) and 50 mg. I. M. (Depo) when anastomosis completed, and 25-50 mg. I. M. (Depo) daily ×3	6	4-9	4 patent 2 thrombosed

* One dog was excluded in which severe infection developed in both wounds. When it was killed, on seventh postoperative day, both anastomoses were thrombosed.

outside diameter) are accompanied by a high incidence of thrombotic occlusion. Hurwitt et al.[3] found that anastomoses between the splenic and mesenteric arteries, even though the dogs had received 1 mg. of heparin per pound, resulted in thrombosis at the anastomosis in 9 of 18 dogs (50%). Shumacker and Lowenberg [4] reported thrombosis at the site of anastomosis in 14 out of 22 canine arteries of 4.0 mm. or less external diameter (an incidence of 64%). A notable exception to this general opinion was expressed by Baker et al.,[5] who felt that "suture technique rather than type of anastomosis or size of the vessel appeared to determine future patency." However, their anastomoses were made in carotid arteries of 14 to 20 kg. dogs, and the outside diameter of the arteries appears to have been determined after the segment of artery had been excised. Their measurements of the arterial segments averaged 3.04 mm. in outside diameter, with the lumen averaging 1.6 mm. in diameter. Most workers would agree that the size of a particular artery decreases markedly after being excised and is in a collapsed state. For uniformity, it would seem preferable in evaluating results of small-artery anastomoses to measure routinely the outside diameter of the artery as soon as it is exposed, and before extensive dissection or excision, since either of these maneuvers significantly decreases the diameter of the vessel. Such early measurements were made in our study and in that of Shumaker and Lowenberg. It is acknowledged that poor surgical technique increases the incidence of thrombosis. However, even with the best surgical technique, there is still a high incidence of thrombosis when dealing with very small arteries.

Electrostatic Field.—It has been shown in experiments by Sawyer and Pate [6] that a potential difference exists in normal blood vessel walls between the intima and the adventitia, the intima being negative in respect to the adventitia. If gross injury occurs, such as transection, crushing, rough dissection, or exposure or drying out, there is a local reversal of the potential difference, the intima becoming positive in respect to the adventitia. It also has been shown by Abramson [7-10] that white blood cells, platelets, and red blood cells are attracted to the positive pole of an electrophoretic cell. The theory was consequently advanced that the injury currents caused by trauma to blood vessel walls and the surrounding tissues may create an electrophoretic force which attracts and holds negatively charged platelets, red blood cells, and white blood cells against the injured vessel wall, thereby promoting thrombosis. The electrostatic field created in our experiment was an effort to overcome the effect of the positively charged intima at the anastomotic line and to prevent this factor from causing thrombotic occlusion. Two hundred fifty volts was delivered to the electrodes surrounding the vessel, and it is presumed that an electrostatic field existed, although our electrical engineer consultants were not able to devise a method to measure its strength. Our negative results using this technique indicate that overcoming this factor alone is not enough to prevent thrombosis, or that this factor was not overcome. A previous attempt by Sawyer and Deutch [11] to modify this potential difference by creating an electric field was only slightly effective.

Modification of End-to-End Anastomosis.

It is probable that some degree of constriction exists at each standard-type, end-to-end anastomosis, if not immediately then subsequently. Even a slight degree of constriction is of significance when is occurs in small vessels.

Arteriographic studies, performed in a few instances, demonstrated considerable constriction at the anastomotic line. The modification used increased the diameter of the anastomosis and would therefore produce less stasis than a standard form of suture. It was hoped that this decrease in stasis would materially reduce the incidence of thrombosis. The results of our study of this technique were disappointing. It would seem that overcoming this factor alone is not sufficient to prevent thrombotic occlusion in small-artery anastomoses.

Distal Arteriovenous Fistula.—It was felt that the rate of blood flow through the anastomotic site would be markedly increased by creating just distal to the anastomosis an arteriovenous fistula. In two animals actual blood flow through the anastomosis, both with and without a distal arteriovenous fistula, was measured, and it was found that, whereas the end-to-end suture did not significantly alter the blood flow, the arteriovenous fistula increased the rate of flow four to seven times. If the rate of blood flow through the site of anastomosis were a critical factor in promoting or deterring thrombosis, the marked increase in flow which accompanies an A-V fistula would be expected to reduce the incidence of thrombosis. Nevertheless, no such effect was observed in these animals. In each instance when the end-to-end anastomosis was thrombosed, the fistula also was thrombosed. We have assumed that thrombosis occurred first at the end-to-end suture and propagated to include the fistula, since we and others have noted practically no difficulty in getting arteriovenous fistulae to remain patent. It was expected that such an increase in rate of blood flow would materially decrease the incidence of thrombosis. Why this did not result is not known. One possible explanation is that the decreased pressure in the artery at the site of end-to-end anastomosis which results from the fistula may lead to a decreased caliber of the artery and a further decrease in the size of the lumen at the end-to-end anastomosis.

Fibrinolysin.—Fibrinolysin is a naturally occurring, proteolytic enzyme of plasma which exerts its major effect on fibrin. This specificity of attack appears related to the fact that fibrin usually absorbs fibrinolysin. It has been shown by others [12,13] that infusion of fibrinolysin will dissolve thrombi. It would seem that this enzmye would have a beneficial effect in vascular surgery in lysing the fibrin deposits at an anastomotic line, thereby preventing thrombosis. The material used in this study was an early preparation, requiring activation by streptokinase, and the optimum dosage has not yet been determined. Villavicencio and Warren [14] have reported lysis of thrombi in vessel grafts by fibrinolysin when given intra-arterially in much larger quantities. Our poor results may have been due to the small amounts of fibrinolysin used. No increase in oozing from the wound was noted in our experiments using fibrinolysin. Others have made the same observation when larger quantities were used. With the more refined preparation now available, further study is needed, using much larger amounts more frequently. If this substance proves effective without causing an increased bleeding tendency, it will have many advantages over heparin or bishydroxycoumarin (Dicumarol).

Heparin.—It was hoped that thrombosis at anastomoses in small vessels could be prevented by means other than the use of anticoagulants. However, our own efforts and those of others have not demonstrated any other effective means of accomplishing this. Anticoagulants can be used with relative safety in operations on peripheral arteries, but their usefulness would be markedly limited in operations within the thorax or peritoneal cavity. The experiments with heparin in this study are of a preliminary nature, the optimum means of controlling the coagulability of the blood not having been determined. The results obtained, however, do indicate that the anastomoses may be kept patent by this means. Kiesewetter and Shumacker [1] demonstrated the greater effectiveness of heparin than of bishydroxycoumarin in preventing thrombosis in small arteries which had been severely traumatized, when treated for a period of five to seven days. They also showed that a single dose of heparin or bishydroxycoumarin appreciably lowered the incidence of thrombosis.

Further study is planned to determine the optimum dosage of heparin, hoping to find an amount and schedule which will prevent thrombosis within the vessel but which will not cause troublesome hemorrhage in the wound.

TABLE 6.—*Summary of Efforts to Prevent Thrombosis*

Group	No. Thrombosed on Experimental Side	No. Thrombosed on Control Side
I. Electrostatic field	9 of 11 (82%)	9 of 11 (82%)
II. Modified anastomosis	5 of 13 (38%)	4 of 13 (31%)
III. Distal A-V fistula	13 of 20 (65%)	12 of 20 (60%)
IV. Fibrinolysin	28 of 42 (67%)	7 of 12 (58%)
V. Heparin	2 of 16 (13%)	23 of 45 (51%)*

* Total of comparable controls in groups II, III, and IV.

A summary of the over-all results achieved in the study appears in Table 6.

Summary

The incidence of thrombotic occlusion of anastomoses in small arteries is high.

Attempts have been made to reduce this incidence by (1) inducing a negative electrostatic field about the anastomosis, (2) enlarging the anastomosis, (3) increasing the rate of blood flow through the anastomosis by means of a distally placed arteriovenous fistula, (4) administering fibrinolysin, and (5) heparinization. Under the conditions of these experiments no benefit was demonstrated by any of these measures except heparinization.

While various factors, such as the current of injury, the presence of constriction at the site of anastomosis, and the rate of blood flow through the anastomosis, are undoubtedly of some importance in determining the ultimate presence or absence of thrombosis, it seems from these experiences that the most important single factor is the coagulability of the blood.

REFERENCES

1. Kiesewetter, W. B., and Shumacker, H. B., Jr.: An Experimental Study of the Comparative Efficacy of Heparin and Dicumarol in the Prevention of Arterial and Venous Thrombosis, Surg. Gynec. & Obst. 86:687-702, 1948.

2. Linton, R. R.: Some Practical Considerations in the Surgery of Blood Vessel Grafts, Surgery 38:817-834, 1955.

3. Hurwitt, E. S.; Altman, S.; Borow, M., and Rosenblatt, M.: Intra-Abdominal Arterial Anastomoses: Experimental Study, Surgery 34: 1043-1060, 1953.

4. Shumacker, H. B., Jr., and Lowenberg, R. I.: Experimental Studies in Vascular Repair, Surgery 24:79-89, 1948.

5. Baker, N. H.; Kirklin, J. W.; Grindlay, J. H., and Edwards, J. E.: Use of Autografts to Bridge Defects in Arteries of Coronary Size, Surgery 44: 548-553, 1958.

6. Sawyer, P. N., and Pate, J. W.: Bio-Electric Phenomena as Etiological Agents in Intravascular Thrombosis, Surgery 34:491-500, 1953.

7. Abramson, H. A.: The Influence of Low Electromotive Force on the Electrophoresis of Lymphocytes of Different Ages, J. Exper. Med. 41:445-450, 1925.

8. Abramson, H. A.: The Possible Relationship Between the Current of Injury and White-Blood Cells in Inflammation, Am. J. M. Sc. 167:702-710, 1924.

9. Abramson, H. A.: The Cataphoretic Velocity of Mammalian Red Blood Cells, J. Gen. Physiol. 12:711-725, 1929.

10. Bigelow, F. S. and Desforges, J. F.: Mobility of Human Platelets in Microelectrophoresis Cells, Am. J. Med. 14:495-496, 1952.

11. Sawyer, P. N. and Deutch, B.: The Experimental Use of Oriented Electrical Fields to Delay and Prevent Intravascular Thrombosis, S. Forum 5:173-178, 1954.

12. Grossi, C. E.; Cliffton, E. E., and Cannamela, D. A.: The Lysis of Intravascular Thrombi in Rabbits with Human Plasmin (Fibrinolysin), Blood 9:310-320, 1954.

13. Cliffton, E. E.; Grossi, C. E., and Cannamela, D. A.: Lysis of Thrombi Produced by Sodium Morrhuate in the Femoral Vein of Dogs by Human Plasmin (Fibrinolysin), Ann. Surg. 139:52-62, 1954.

14. Villavicencio, J. L., and Warren, R.: The Use of Plasmin for Intraoperative Lysis of Clots Occurring During Experimental Arterial Surgery, S. Forum 1958, to be published.

DISCUSSION

DR. WALTER J. BURDETTE, Salt Lake City: Dr. Engler and his colleagues are to be congratulated on their scholarly studies. Among the limitations of the methods described is the manual nature of the suturing. A number of refined stapling instruments which have been developed at the Institute of Surgical Instruments in Moscow were demonstrated to me in several institutions in the Soviet Union last summer. I was particularly impressed with the possibilities of the instrument designed to anastomose blood vessels, even though it is small, expensive, and elaborate. The ends to be anastomosed are everted as a cuff after the vessel is

occluded with serratiform jaws, and the anastomosis is made in a single compressive motion. Some of the difficulties described in the paper which has been presented could possibly be resolved through the use of this or a similar instrument.

DR. EDWIN J. WHITMAN, Rochester, Minn.: My question pertains to the late status of these grafts. Do you feel that thrombosis occurs most frequently in the first 24 to 48 hours following surgery? Did you follow for several months any of the animals whose grafts remained patent several days following surgery, to determine what percentage remained patent in the later postoperative period?

DR. HAROLD LAUFMAN, Chicago: I think a very important aspect of this work is its negative nature. There has been a great deal of testimonial evidence in the recent past in favor of fibrinolysin as a solvent of clots. We have never become enthused over the ability of fibrinolysin either to dissolve or to prevent clotting when used alone, either experimentally or clinically. On the theoretical basis that a part of the thrombogenic trauma at time of surgery is exposure of the intima to the drying effects of air during the suturing process, we are experimenting with the feasibility of doing an anastomotic procedure on small vessels under constant spray of heparin solution, never allowing air to dry the intima at any time. We are at present devising a technique to accomplish this in the hope that it, together with other refinements, may aid in the prevention of thrombosis after suturing of small vessels.

DR. WILLIAM HENRY MORETZ, Augusta, Ga.: We felt that increasing the blood flow tremendously would show some benefit by reducing the incidence of thrombosis. Such, however, was not the case, indicating that the problem probably is subject to solution only by means of doing something that will affect the blood, either by keeping it from clotting or by dissolving the clot as it forms.

Dr. Engler mentioned the optimum doses of heparin. However, it might be that there is no such thing as an optimum dose of heparin for this purpose. It may be that the minimum amount of heparin required to keep the anastomosis open would be dangerous if surgery was being done within the abdomen or the thorax. For this reason, and because of the very encouraging results reported last week at a seminar on the use of fibrinolysin, which Dr. Engler attended, we plan to pursue this particular attempt further using much larger doses of fibrinolysin, which were reported to be quite effective in dissolving thrombi without at the same time producing troublesome hemorrhage from the wound.

It is hoped that by this means we may be able to keep the anastomosis open without running the additional risk of hemorrhage from the wound.

DR. HAROLD S. ENGLER, Augusta, Ga.: In answer to the question concerning observation of the grafts over a long period of time: In the first, and only, series in which we used the grafts, we found that most of them became occluded very early—in fact, before closure of the wounds. Then we went on to investigate simple anastomoses, and the problem that we have worked on here is the immediate thrombosis that occurs, and that usually occurs early because of the factors mentioned. We think, too, that if a homograft does not become thrombosed early (and this work has been done on the aorta) there may be late thrombosis that occurs because of other factors that exist locally and in relationship to the graft, such as the immune response and the growth of fibrous tissue into the graft.

I wish to thank the discussers, and I think the suggestion that one should prevent air from coming in contact with the intima as a possible factor in thrombosis might well have merit. I would like to express my appreciation for the privilege of participating in this meeting. It has been most enjoyable.

Bleeding Varices Due to Cirrhosis

Survival After (1) Nonsurgical Treatment, (2) Splenectomy With or Without Omentopexy, and (3) Portacaval and Splenorenal Shunts

GEORGE A. HALLENBECK, M.D.; MORTON S. COMESS, M.D.; ERIC E. WOLLAEGER, M.D., and ROBERT P. GAGE, M.S., Rochester, Minn.

Evidence exists that splenorenal and portacaval shunts decrease the frequency and severity of bleeding from esophagogastric varices in patients who have cirrhosis of the liver.[2,3,6,7,12] It has been more difficult to evaluate the effectiveness of these operations in prolonging the lives of such patients.[3,7,13]

General Background

Several studies have shown the seriousness of bleeding from the gastrointestinal tract in patients with cirrhosis of the liver. Ratnoff and Patek,[16] as well as Nachlas and associates,[13] found that only 28% of such patients survived for one year after the first hemorrhage. Douglass and Snell[5] found that 54% survived at least one year after the first episode of bleeding; however, the circumstances of their practice demanded that most of their patients had to survive the first hemorrhage in order to reach them. The fate of those who survived the first year was more encouraging. From the end of the first year to the end of the fifth year, the percentage of surviving patients decreased modestly from 28% to 20% in the series of Ratnoff and Patek[16] and from 54% to 31% in that of Douglass and Snell.[5]

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Section of Surgery, Mayo Clinic and Mayo Foundation (Dr. Hallenbeck). Fellow in Surgery, Mayo Foundation, (Dr. Comess). Section of Medicine (Dr. Wollaeger); Section of Biometry and Medical Statistics (Mr. Gage), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Survival rates after portacaval or splenorenal shunts have been much better than those in nonsurgical patients.[6,7] At first glance, one might be tempted to give the operations full credit for this apparent improvement. However, it has been pointed out by several authors that patients with cirrhosis of the liver who have shunts instituted are highly selected and cannot be compared with the unselected patients having cirrhosis who bleed and who make up the series treated without operation.[3,7,13] The operative mortality rate for shunts is so high for patients having seriously impaired hepatic function (as evidenced by chronic intractable ascites or pronounced abnormality in results of tests of hepatic function) that the operations ordinarily are not advised for such patients. Many cirrhotic patients who bleed fall into this category; some promptly go into hepatic coma and die with the first hemorrhage. All such patients are found in series of unselected patients with cirrhosis who bleed, but most of them are excluded from series of patients selected for shunt procedures. If it happened to be true that the methods of selecting patients for portacaval shunting unintentionally, but automatically, excluded most patients destined to die within a year after the first hemorrhage, while including most of those otherwise destined to survive that year, the shunts, provided they did no harm, would appear falsely to increase survival.

Material and Methods

Needed for comparison with studies of groups of patients who have shunts is a follow-up study of patients comparable in

other respects but who did not have the operation. In an attempt to obtain such information, we reviewed the records of many patients examined at the Mayo Clinic in past years who had cirrhosis of the liver and who had vomited blood, hoping to be able to distinguish those who met the criteria currently used to select patients for portacaval shunts from those who did not. We were unable to carry out this intention, partly because the data available in earlier years did not permit as accurate an appraisal of hepatic function as is usually carried out now, but mostly because many patients who today would be candidates for shunts underwent splenectomy, often with omentopexy. It was evident that these latter patients had been selected carefully in order to eliminate many for whom the operative risk would have been excessive. As a group, patients with cirrhosis of the liver who had splenectomy at the Clinic appeared to be similar to those now being treated by shunt procedures. For this reason, we decided to compare the results of operation in these two groups of patients.

Records were examined of all patients who had splenectomy at the Clinic between 1909 and 1947 in whom the diagnosis of cirrhosis of the liver, Banti's syndrome, or splenic anemia was recorded. Two criteria were used to select patients for this study, namely, (1) a history of bleeding from the gastrointestinal tract before splenectomy was performed and (2) an irrefutable diagnosis of cirrhosis of the liver. The surgeons' description of the liver in such fashion as "hobnailed," grossly nodular, or cirrhotic was accepted as suitable evidence for cirrhosis. Laboratory data, available in the later years covered by the study, were taken into account. If any question existed concerning the validity of the diagnosis of cirrhosis, the case was excluded from the study. A total of 75 patients satisfied these criteria; in 24 of them omentopexy had been performed together with the splenectomy.

A group of 54 patients having cirrhosis of the liver who bled preoperatively but who had had either splenorenal or direct portacaval shunts constructed from one to six years previously was studied as well. These patients were selected for operation according to the criteria recommended by Linton.[9]

Results

Some general data concerning these two groups of patients and emphasizing the many similarities between them are presented in Table 1. Some differences are seen as well. The average age of patients who had splenectomy (36 years) was less than that of patients having shunts (47 years). Fewer of the splenectomy group (8%) had a known history of alcoholism than was true of the group with shunts (32%). The distribution of patients by sex, the history of bleeding before operation, and the incidence of transient ascites before operation were similar in the two groups. Data collected preoperatively concerning the percentage of retention of sulfobromophthalein U. S. P. dye (Bromsulphalein) one hour after its injection were available for 50 of the 75 patients who had splenectomy; the total serum bilirubin was known in 48 of these patients. Thus, in Table 1, the two series of patients are compared with respect to the incidence of degrees of impairment of excretion of sulfobromophthalein and of increase in serum bilirubin. In both respects, the patients who had splenectomy appear remarkably similar to those who had shunts. Fewer patients with splenorenal shunts had serious impairment of excretion of sulfobromophthalein or an increase of serum bilirubin to more than 2 mg. per 100 ml. than was the case for patients having direct portacaval shunts.

We interpret the objective data we were able to obtain as reinforcing the impression, gained from study of individual records, that the patients who underwent splenectomy and those who had shunts constructed were similar with respect to a history of bleeding and to the severity of their hepatic disease.

The two groups of patients then were compared with respect to survival rates

TABLE 1.—*General Comparison of Seventy-Five Cirrhotic Patients Who Had Splenectomy with Fifty-Four Cirrhotic Patients Who Had Shunts*

	Splenectomy (75 Cases)	Shunt Operations		
		Total (54 Cases)	Portacaval (33 Cases)	Splenorenal (21 Cases)
Age, yr.: Youngest	4	5	5	27
Oldest	63	73	73	66
Mean	36	47	47	46
Sex: Males, %	63	59	55	67
Females, %	37	41	45	33
Known alcoholic history, %	8	32	36	24
Preoperative bleeding				
Hematemesis, %	96	96	94	100
Melena only, %	4	4	6	0
No. of hemorrhages before operation, %				
1	32	22	18	29
2-4	44	52	52	52
5-7	9	11	15	5
>7	11	15	15	14
Not certain	4	0	0	0
No. of years between first hemorrhage and operation, %				
<1	54	61	58	67
1-5	28	30	27	33
>5	15	9	15	0
Not certain	3	0	0	0
Ascites before operation, %				
None	73	72	79	71
Transient	27	28	21	29
Chronic	0	0	0	0
Sulfobromophthalein retention before operation, %				
None	24 *	11	9	14
1-10	32	34	22	52
11-22	28	38	44	29
23-40	14	15	22	5
>40	2	2	3	0
Total serum bilirubin (mg/100 ml.) before operation, %				
0-1.0	44 †	43	46	38
1.1-1.5	29	30	21	43
1.6-2.0	8	13	9	19
2.1-3.0	8	7	12	0
>3.0	11	7	12	0

* Data in this column are from 50 patients.
† Data in this column are from 48 patients.

and the incidence of bleeding after operation. Survival rates were calculated by the actuarial method. This technique has been described in detail by Berkson and Gage.[1] The actuarial survival rates thus determined differ from the ordinary survival rates established by the usual direct method. These actuarial rates allow one to estimate the probability of survival at a certain period of time after operation if all patients had been operated on sufficiently early to be eligible to survive to the time in question.

For the first five years after operation, the survival curve for 73 traced patients who had splenectomy with or without omentopexy but who had no shunt did not differ significantly from that for 54 patients having splenorenal or portacaval shunts (Fig. 1). On an actuarial basis, of those having splenectomy without a shunt, 40% survived 10 years and 19% survived more than 15 years after operation (Table 2).

When the 21 patients with splenorenal shunts and the 33 with end-to-side portacaval

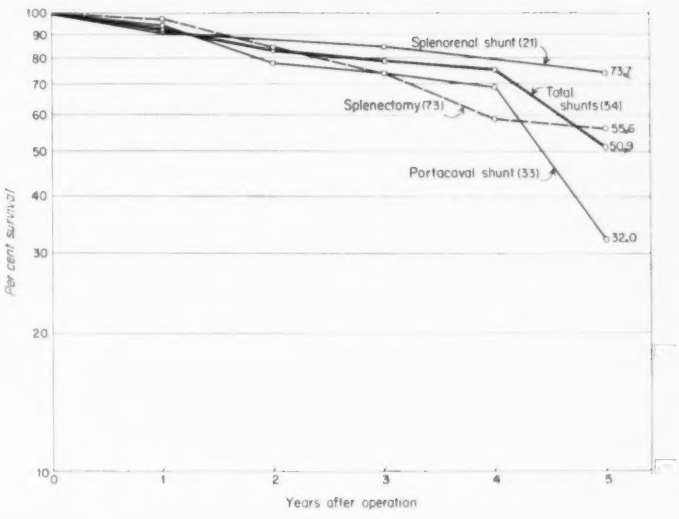

Fig. 1.—Actuarial survival curves for cirrhotic patients who experienced gastrointestinal bleeding preoperatively and who underwent splenectomy or a shunting operation.

shunts were analyzed separately, survival curves for splenorenal shunts were slightly better than those for portacaval shunts for the first four years and much better at the end of five years—74%, as compared with 32% (Fig. 1). The number of patients eligible to survive five years is so small that more time must pass before the significance of the apparently poorer survival of patients with portacaval shunts during the fifth year can be evaluated (Table 3).

Much more bleeding was present during the years after operation in those who had splenectomy than in those who had shunts (Table 4). At least two-thirds of those with splenectomy bled, whereas only 20% of those with shunts bled. Similarly, at least 46% of those who later died after surviving splenectomy were known to have bled from the gastrointestinal tract at the time of death, whereas only 18% of those with shunts who died subsequently bled at

TABLE 2.—*Bleeding from Esophagogastric Varices in Cirrhosis: Actuarial Survival Rates After Splenectomy*

Interval Following Hospital Dismissal, Yr.	Status at Last Report		Total Persons Living at Beginning of Interval	Persons, Adjusted	Probability of Dying in Interval	Actuarial Survival Rate, %
	Dead	Living				
0-1	2	..	73	73	0.0274	100.0
1-2	10	1	71	70.5	0.1418	97.3
2-3	7	0	60	60	0.1167	83.5
3-4	11	0	53	53	0.2075	73.7
4-5	2	0	42	42	0.0476	58.4
5-6	2	0	40	40	0.0500	55.6
6-7	5	1	38	37.5	0.1333	52.9
7-8	4	1	32	31.5	0.1270	45.8
8-9	0	2	27	26	..	40.0
9-10	0	0	25	25	..	40.0
10-11	2	2	25	24	0.0833	40.0
11-12	4	0	21	21	0.1905	36.7
12-13	1	0	17	17	0.0588	29.7
13-14	4	1	16	15.5	0.2581	27.9
14-15	1	0	11	11	0.0909	20.7
15+	5	5	10	..	..	18.8

TABLE 3.—*Bleeding from Esophagogastric Varices in Cirrhosis: Actuarial Survival Rates After Shunts*

Interval Following Hospital Dismissal, Yr.	Status at Last Report		Total Persons Living at Beginning of Interval	Persons, Adjusted	Probability of Dying in Interval	Actuarial Survival Rate, %
	Dead	Living				
			Portacaval Shunts			
0-1	2	--	33	33	0.0606	100
1-2	5	5	31	28.5	0.1754	93.9
2-3	1	1	21	20.5	0.0488	77.5
3-4	1	9	19	14.5	0.0690	73.7
4-5	4	3	9	7.5	0.5333	68.6
5+	--	2	2	--	--	32.0
			Splenorenal Shunts			
0-1	2	--	21	21	0.0952	100
1-2	0	2	19	18	--	90.5
2-3	1	5	17	14.5	0.0690	90.5
3-4	0	3	11	9.5	--	84.2
4-5	1	0	8	8	0.1250	84.2
5+	--	7	7	--	--	73.7
			Total Shunts			
0-1	4	--	54	54	0.0741	100
1-2	5	7	50	46.5	0.1075	92.6
2-3	2	6	38	35	0.0571	83.1
3-4	1	12	30	24	0.0417	78.4
4-5	5	3	17	15.5	0.3226	75.1
5+	--	9	9	--	--	50.9

the time of death. The interval between operation and the first hemorrhage thereafter for those who bled is shown in Table 5. Eight of the eleven patients who bled after shunts did so during the first two years after operation; one bled during each of the succeeding three years. The year of onset of postoperative bleeding among 50 patients who bled after splenectomy was known for all but 5. Of these 45 patients, all but 7 (16%) bled within five years after the operation. If patients with shunts behave similarly, most of those destined to bleed should do so within five years after operation.

Thus, the data indicate that (1) the survival rate for the first five years for the patients having splenorenal or portacaval shunts was similar to that for patients having splenectomy and (2) the incidence of gastrointestinal bleeding subsequent to operation was much greater in patients who had splenectomy without shunts than it was in patients who had shunts.

Comment

Blakemore,[2] Child,[3] and Palmer[14] and associates are among those who have published enough information concerning the survival of patients having cirrhosis of

TABLE 4.—*Comparison of Postoperative Bleeding in Cirrhotic Patients After Splenectomy and After Shunts*

Operation	Patients	Postoperative Hematemesis or Melena or Both, % of Patients			Patients Dead	Hemorrhage at Time of Death, % of Dead Patients		
		Bled	Did Not Bleed	Uncertain		Yes	No	Uncertain
Splenectomy	75	67	24	9	61	46	23	31
Shunts								
Splenorenal	21	14	86	0	4	0	100	0
Portacaval	33	24	76	0	13	23	77	0
Total	54	20	80	0	17	18	82	0

TABLE 5.—*Bleeding from Esophagogastric Varices in Cirrhosis: Interval Between Operation and First Hemorrhage Thereafter*

Time of First Bleeding, Years After Operation	Splenectomy		Splenorenal and Portacaval Shunts	
	Patients	Per Cent *	Patients	Per Cent
0-1	15	33	5	46
1-2	15	33	3	27
2-3	1	2	1	9
3-4	3	7	1	9
4-5	4	9	1	9
5+	7	16	--	--
Unknown	5	--	--	--
Total	50	100	11	100

* Of the 45 patients for whom the interval was known.

the liver who withstood construction of portacaval or splenorenal shunts that survival curves could be calculated from their data. These and our data are presented in Figure 2, together with a curve calculated from the combined data. This last curve, representing the experience of four groups of surgeons with 243 patients, probably gives a good estimate of what can be expected from a mixed group of patients with portacaval and splenorenal shunts during the first five years after operation. We have used it for this purpose in Figure 3, which also shows survival curves for our

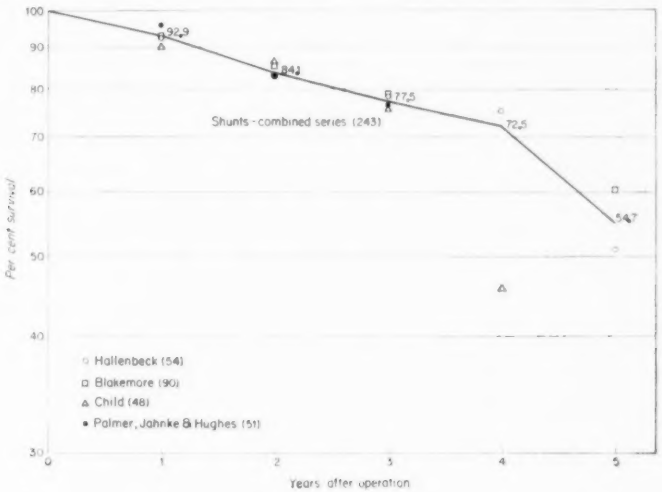

Fig. 2.—Composite actuarial survival curve representing four series of cirrhotic patients having shunting procedures.

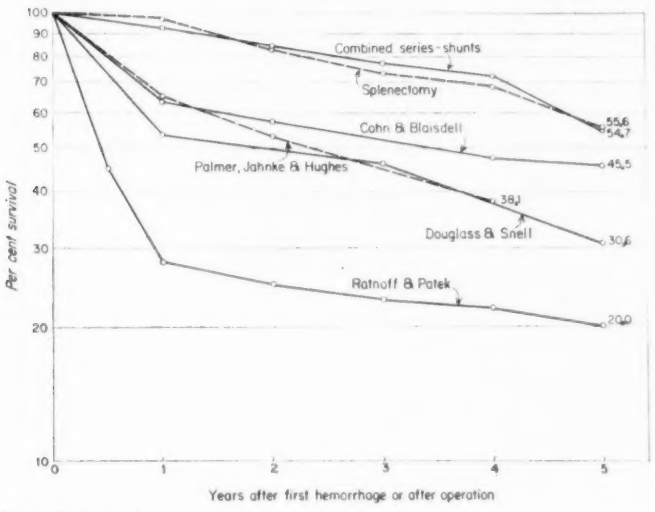

Fig. 3. — Comparative actuarial survival curves of surgical and nonsurgical patients with cirrhosis of the liver who experienced bleeding from the gastrointestinal tract.

group of patients who had splenectomy without performance of a shunt and for four groups of patients with cirrhosis of the liver who had not undergone operation, the data for which were obtained from the publications of others.

The data of Ratnoff and Patek [16] were mentioned earlier in this paper. Their comments about the survival curve that they obtained deserve repetition:

> [It] reveals the period of survival after the first hematemesis in these patients. Forty per cent died within one month of this episode. Indeed, most of these patients died within a week of the initial hematemesis. An additional 30 per cent died by the end of the first year. Thereafter the slope of the curve is almost flat, indicating that if the patient survives one year after hematemesis there is a good chance of his surviving 2, 3 or 4 years. Clinical observations bear this out. There would seem to be a group of patients who die from hematemesis when other signs of liver failure are prominent, such as jaundice, ascites and torpor. In this group, the episode of hematemesis appears suddenly as a "coup de grâce" among these other signs of impending failure. These patients largely comprise the 40 per cent who die shortly after the first hematemesis. However, there remains a second group of patients who in other respects are vigorous and in whom Laennec's cirrhosis is latent and unsuspected until hematemesis occurs. For such patients the hematemesis is a vascular accident which usually is survived if transfusions are promptly given. In this latter group, hematemesis does not appear to reflect a failure of liver parenchyma, but rather a selective weakness in the vascular structure.

Douglass and Snell,[5] like Ratnoff and Patek,[16] included all their 71 patients with cirrhosis of the liver who bled from the gastrointestinal tract, with no effort to select those suitable for surgical treatment; as already noted, they found that 54% lived at least one year after the first hemorrhage. As previously mentioned, this group differs from that of Ratnoff and Patek in that most patients who bled had already survived the first hemorrhage before arriving at the Mayo Clinic. As Douglass and Snell [5] stated:

> Of the 71 patients with gastro-intestinal bleeding 17 arrived at the clinic within one month after the first recognized hemorrhage. The other 54 reported having had their first hemorrhage an average of seventeen months earlier (ranging from one month to ten years). It is apparent that these latter patients actually represent in general the group which has survived the first critical year after occurrence of hemorrhage from esophagogastric varices.

Palmer and co-workers [14] presented a group of 48 patients for whom a portacaval shunting operation was recommended, but not performed for various reasons. Although all these patients had esophageal varices, only half had bled before operation was recommended. In this respect, the series differs from other series of patients we shall consider. A total of 29 of their patients bled during the period of follow-up, including 12 who had not bled previously. A survival curve calculated from the data of Palmer's group by the actuarial method is shown in Figure 3.

Cohn and Blaisdell [4] approached the problem by selecting from a group of 456 cirrhotic patients who bled massively those who they considered would have been acceptable for portacaval anastomosis. Thus, 338 patients who died after the first hemorrhage were eliminated; only 40 of the remaining 118 patients were judged suitable for operation. A survival curve calculated by the actuarial method for the 36 of these 40 patients who could be followed is shown in Figure 3. Further bleeding was common in this group of patients; 32 bled more than once, and 14 of the 23 who died bled at the time of death.

The six survival curves in Figure 3 fall into three groups that differ from one another chiefly with regard to the percentage of patients dying within the first year after observation began. Once the first year has passed, the rate of decline for all the curves is roughly similar.

The two curves deduced from data considered by their authors to be from patients who were candidates for portacaval shunts but who had no operation show only slightly better survival than does the curve from the data of Douglass and Snell,[5] whose chief factor of selection was the fact that most of their patients already had survived the first hemorrhage. The fact that patients who died with the first hemorrhage were

eliminated from these three series of patients is enough to account for the difference between them and those represented by the survival curve obtained from the data of Ratnoff and Patek.[16]

The survival curves for the 73 traced patients who had undergone splenectomy studied by us and for the 243 collected patients with portacaval and splenorenal shunts appear to be the same and show better results than do curves for patients treated without operation. Two facts must be kept in mind when these curves are being compared with those for nonsurgical patients. First, the data are based on patients who survived the operations. The hospital mortality rate for splenectomy done for congestive splenomegaly at the Clinic over the years has been about 10%[11,15]; the same figure is a fair one to assign to portal-venous shunts, better and poorer results having been reported. To describe survival rates for all patients operated on, the curves for those having operations would have to be lowered by approximately 10% to allow for those who did not survive the operation.

The second fact to remember is that survival was computed from the time of the first hemorrhage in those who did not have an operation and from the time of the operation in those who had surgical treatment. Many who had operations had experienced their first hemorrhage months, or even several years, previously (Table 1). If their survivals were computed from the time of the first hemorrhage, the results would be better than the curves in Figure 3 indicate. However, these patients *had* to survive from the time of their first hemorrhage until the time of operation in order to be included in the series of patients who had operations. This serves to emphasize another factor of selection that favored longevity of the patients who were treated surgically. Before being chosen for operation, they had survived the first hemorrhage, and often the first year after it, a period during which patients with cirrhosis of the liver frequently die. This unconscious selection of patients must be added to the conscious exclusion of "poor-risk" patients commonly practiced in selecting candidates for operation.

The conclusion that selection of cases is the most important factor determining the survival curves in Figure 3 is unavoidable. Cirrhosis of the liver is a disease that often pursues a long course, with slow changes. In its early stages, it can be latent clinically; indeed, hemorrhage may be the first suggestion that disease is present. In other cases, bleeding may never occur, or may appear only terminally, when death from hepatic insufficiency is imminent. The patient who has bleeding from varices early in the long history of his disease, when hepatic reserve is still adequate, has a much better chance of living than the one who bleeds only late in the course of the disease. In our opinion, the common methods of selecting patients for operation have screened out most of those patients who are not likely to live long and have included many patients who are particularly likely to survive several years.

Even if this premise is granted, the surprising observation that splenectomy was followed by survival comparable with that after shunts demands explanation. The apparent success of splenectomy with regard to survival occurred despite the fact that the operation had a poor record for prevention of bleeding. This is all the more remarkable in view of the fact that many of those treated by splenectomy had their operations and subsequent bleeding in an era before blood banks existed and when transfusions of blood were used less freely than is now the case. Patients with shunts had a much smaller incidence of postoperative bleeding; yet their curve of survival was similar. Such results might be obtained if the group of patients having splenectomy really had much better preoperative hepatic function than did the group having shunts. It is, of course, impossible to have two groups of patients exactly similar in all respects, but, in the present instance, comparison of the data we were able to assemble

strongly supports the idea that these two groups of patients had a great deal in common and gives no support to the thesis that their differences were great enough to explain the excellent survival of those having splenectomy, despite a poor record with respect to bleeding after operation.

An older concept of the pathogenesis of cirrhosis of the liver associated with bleeding esophagogastric varices held that toxins from the spleen reaching the liver contributed to the hepatic disease. Removal of the spleen was considered to be beneficial by arresting this process. Acceptance of this view would credit splenectomy with preventing progression of the cirrhosis. We know of no data to support this idea and consider that it has been correctly abandoned.[8]

The dilemma would be resolved if it were true that bleeding, although commonly lethal when it occurs in patients having cirrhosis with severe impairment of hepatic function, is well tolerated if the hepatic reserve is good. When the patient with extremely poor hepatic function bleeds and dies, hepatic coma often occurs so promptly that it is difficult to be certain whether exsanguination or hepatic insufficiency was the principal cause of death. The highly selected groups of patients who are chosen for surgical treatment and survive the operations might survive hemorrhage short of exsanguination simply because hepatic insufficiency does not develop readily in these patients. In our judgment, this is one of the factors involved in causing the survival curve for patients after splenectomy to resemble that for patients after shunts, despite more frequent bleeding. It appears unreasonable that this could be the sole explanation. Some people with esophagogastric varices do become exsanguinated, and this should have occurred with a sufficiently increased frequency among patients with splenectomy (at least two-thirds of whom bled) than among patients with shunts (of whom one-fifth bled) to cause superior survival rates for patients having shunts.

Could some other factor be operating simultaneously to limit survival of the patients who had shunts? Could shunts hasten hepatic deterioration and, if so, could portacaval and splenorenal shunts do so in different degree? It has been difficult to obtain the answer to the first question because some deterioration of hepatic function, rapid or slow, is characteristic of the natural history of cirrhosis of the liver, whether or not shunts are instituted. Comparison of the results of tests of hepatic function performed before and at intervals of up to 42 months after construction of many of our splenorenal and portacaval shunts has been published elsewhere.[7] Data of this type offered no proof that hepatic function deteriorated with unusual rapidity during the first few years after operation. Ellis and associates[6] came to a similar conclusion. These authors, however, found that a much larger number of their patients with portacaval shunts (41%) died during the time of follow-up than was the case with patients subjected to splenorenal shunts (24%). They went on to state:

> This difference in mortality, as well as a similar morbidity in our patients after portacaval shunts, has made us prefer to do the splenorenal shunt when possible in spite of the fact that recurrent bleeding was slightly more frequent in the splenorenal group.

In our experience, reported elsewhere,[7] neurologic dysfunction, sometimes called "portal-systemic encephalopathy," is not unusual after end-to-side portacaval shunt. However, we have yet to see it after splenorenal shunts, and we know of only one such case reported in the literature.[10] The five-year actuarial survival rate of 74% that followed our splenorenal shunts was much better than the values of 32% for our patients with portacaval shunts and 56% for patients having splenectomy without any shunt (Fig. 1). Again, more time must pass before the significance of this difference can be assessed. Our hospital mortality rate after splenorenal shunt, which is currently 6%, has been less than the rate after portacaval shunt or splenectomy without shunting.

It would be helpful to compare survival curves over longer periods for other, larger series of patients who have been treated by these operations. It is possible to make calculations for actuarial survival curves from data in the literature only when the length of follow-up for each patient and the status, living or dead, at that time are given or can be deduced.

Meanwhile, physicians must have some program of treatment for these patients that is in harmony with the information at hand. It appears realistic to accept the observation that the apparent increased rate of survival after either splenectomy or shunts results principally from selection of cases and to believe that less bleeding from varices follows shunt operations than occurs after splenectomy alone. Our experience suggests, but cannot prove, that splenorenal shunts are followed by a better survival rate than are end-to-side portacaval shunts. Portal-systemic encephalopathy certainly is seen more frequently after production of an Eck fistula than it is after splenorenal anastomosis is performed. It appears to us that efforts to limit bleeding from varices in these patients are sufficiently worth while to justify operation in selected cases. With these points in mind, we currently employ splenectomy with end-to-side splenorenal shunt when it is indicated and possible for patients having cirrhosis of the liver who have bled from esophagogastric varices. We look forward to the time when this course of action can rest more securely on experimental data or be changed, as the case may prove to be.

Summary and Conclusions

A total of 75 patients having cirrhosis of the liver who bled from the gastrointestinal tract before operation and who had splenectomy with or without omentopexy and a group of 54 similar patients who had splenorenal or portacaval shunts were compared with respect to survival rates and the incidence of gastrointestinal bleeding after operation.

Survival rates for both groups of patients during the first five years were similar. A much greater incidence of postoperative bleeding was noted in the group that had splenectomy than in those treated by portal-venous shunts.

Survival rates for patients who underwent splenectomy or portacaval shunts were compared with those for four published series of patients with gastrointestinal bleeding associated with cirrhosis of the liver who did not have surgical treatment. The argument was developed that the principal reason for better survival in the surgical groups is that the methods used to select patients for operation also select those most likely to survive longest.

This study suggests that splenectomy with end-to-side splenorenal anastomosis gives results superior to those after either splenectomy alone or end-to-side portacaval anastomosis. More data and a longer period of observation are needed to establish this point beyond question or to disprove it.

Mayo Clinic.

REFERENCES

1. Berkson, J., and Gage, R. P.: Calculation of Survival Rates for Cancer, Proc. Staff Meet. Mayo Clin. 25:270-286 (May 24) 1950.

2. Blakemore, A. H.: Portacaval Shunting for Portal Hypertension, Surg. Gynec. & Obst. 94:443-454 (April) 1952.

3. Child, C. G., III: The Portal Circulation, New England J. Med. 252:837-850 (May 19) 1955.

4. Cohn, R., and Blaisdell, F. W.: The Natural History of the Patient with Cirrhosis of the Liver with Esophageal Varices Following the First Massive Hemorrhage, Surg. Gynec. & Obst. 106:699-701 (June) 1958.

5. Douglass, B. E., and Snell, A. M.: Portal Cirrhosis: An Analysis of 444 Cases with Notes on Modern Methods of Treatment, Gastroenterology 15:407-425 (July) 1950.

6. Ellis, D. S.; Linton, R. R., and Jones, C. M.: Effect of Venous-Shunt Surgery on Liver Function in Patients with Portal Hypertension: A Follow-Up Study of 125 Patients Operated on in the Last 10 Years, New England J. Med. 254:931-936 (May 17) 1956.

7. Hallenbeck, G. A., and Shocket, Everett: An Evaluation of Portacaval Shunts for Portal Hypertension, Surg. Gynec. & Obst. 105:49-60 (July) 1957.

8. Howells, L.: Treatment of Splenic Anæmia and Banti's Syndrome, Lancet 1:1320-1324 (June 11) 1938.

9. Linton, R. R.: The Selection of Patients for Portacaval Shunts, Ann. Surg. 134:433-443 (Sept.) 1951.

10. McDermott, W. V., Jr.; Adams, R. D., and Riddell, A. G.: Ammonia Metabolism in Man, Ann. Surg. 140:539-556 (Oct.) 1954.

11. Miller, E. M., and Hagedorn, A. B.: Results of Splenectomy: A Follow-Up Study of 140 Consecutive Cases, Ann. Surg. 134:815-821 (Nov.) 1951.

12. Nachlas, M. M.: A Critical Evaluation of Venous Shunts for the Treatment of Cirrhotic Patients with Esophageal Varices, Ann. Surg. 148: 169-183 (Aug.) 1958.

13. Nachlas, M. M.; O'Neil, J. E., and Campbell, A. J. A.: The Life History of Patients with Cirrhosis of the Liver and Bleeding Esophageal Varices, Ann. Surg. 141:10-23 (Jan.) 1955.

14. Palmer, E. D.; Jahnke, E. J., and Hughes, C. W.: Evaluation of Clinical Results of Portal Decompression in Cirrhosis, J. A. M. A. 164:746-748 (June 15) 1957.

15. Pemberton, J. deJ., and Kiernan, P.: Surgery of the Spleen, S. Clin. North America 25:880-890 (Aug.) 1945.

16. Ratnoff, O. D., and Patek, A. J., Jr.: The Natural History of Laennec's Cirrhosis of the Liver, Medicine 21:207-268 (Sept.) 1942.

DISCUSSION

DR. ORMAND C. JULIAN, Chicago: I wasn't really thinking about having a different plan—I was complimenting in my mind Dr. Hallenbeck's handling of the tremendously complex problem and, I think, joining him in a little bit of despair that at the end of a number of years of experience in a great many centers we really don't know the answer to the kind of surgery that should be applied to patients with esophageal varices who bleed. Indeed, we don't know whether the surgery of various kinds we have applied has really been any good. Our clinical material has made me very much aware of a factor of alcoholism as being overwhelmingly important in the survival of patients, whether they are operated on or are not. This fundamental background of the patient, whether he can abstain from alcohol and therefore protect his liver, or whether he cannot, simply overwhelms in importance every other factor of surgical treatment except the actual success in reducing the portal pressure by a shunt operation. If we could assume that all shunts did what they are supposed to do, that is, stay open and reduce permanently the portal pressure, I believe the only factor gauging the survival of the patient would be whether he could abstain from alcohol—and, of course, whether his liver disease was or was not too far advanced for his permanent recovery.

DR. JACOB K. BERMAN, Indianapolis: I have enjoyed Dr. Hallenbeck's paper, for he is seeking to determine the natural course of the disease as opposed to the course of the disease which has been altered by empirical therapeutic measures. There is one danger in this, and that is that we must not become therapeutic nihilists.

I would like to pose two questions, which I wrote down as he was giving his paper. First of all, if the cirrhotic liver depends upon the spleen as a reservoir when it can no longer respond to the continued variations in portal blood volume, then theoretically, at any rate, removing the spleen should increase the portal hypertension and should increase the dangers of hemorrhage and of ascites and all other complications. Does he believe that the portal bed takes over, so to speak, this reservoir function through its many collateral channels? Second, I should like to ask him whether or not he has done any studies to determine whether bleeding varices are, in fact, venous or arteriovenous bleeders.

A good many years ago I presented a paper before the Wisconsin State Medical Society concerning oxygen saturation difference studies in the systemic arterial and venous blood, the arterial and portal-venous blood, and the arterial and hepatic-venous blood. Our findings were summarized as follows:

"Although the oxygen content, capacity volume, and saturation index varied greatly under various conditions, the arteriovenous difference furnished reliable evidence of a constant increase in the normal from mesenteric to hepatic veins. The cirrhotic showed less arterio-portal-venous difference and more arterio-hepatic-venous difference. This was interpreted as indicating: (1) arterio-portal-venous shunts involving the entire splanchnic bed; and (2) oxygen desaturation due to sluggish flow, utilization by the ischemic liver, and diffusion through collaterals" (*Wisconsin M. J.* 51:1175 [Dec.] 1952).

Later I studied the problem in animals and in man by injecting sodium fluorescein in the hepatic artery and observing its appearance in portal venous branches under ultraviolet light. All subjects had arm-to-lung-to-tongue circulation time as well. The material appeared in

portal branches in less time than the arm-to-lung or arm-to-tongue interval, again indicating a bypass mechanism of the hepatic and mesenteric capillary beds. Also, at the time of operation small portal-vein branches, when divided, often spurt in a pulsatile fashion. This also indicates arteriovenous communications through larger-than-capillary tributaries. Could it be, then, that we are looking at this problem from the wrong angle? Could it be that in fact we are having bleeding varices because we have enormous arteriovenus shunts throughout the entire portal bed?

DR. GEORGE A. HALLENBECK, Rochester, Minn.: Dr. Julian emphasized the importance of alcoholism as an influence on the results of portacaval shunting, and in general as an influence on the condition of patients who have cirrhosis and who have bled. Certainly, in the patient who is alcoholic this seems to be a very important consideration. As Dr. Julian concluded his discussion and sat down, we chatted for a moment about it. It became clear that the patients he sees are more frequently alcoholic than the ones we see. If you will remember, fewer than one-third of those in whom we established shunts appeared to have a history of alcoholism. Also, in that regard, I had the impression that alcoholics seemed to get along a little better in respect to operative mortality than some of the patients who had had hepatitis and postnecrotic cirrhosis as the basis of their trouble. I was visiting Gardner Child in Boston on one occasion, and we talked about this. I suggested that view to him, and he said: "That is very interesting. I had exactly the reverse view from seeing patients on whom I have operated. It seems to me that the people who had postnecrotic cirrhosis really got along much better." I may have drawn my conclusions from too small a number of cases.

Dr. Berman's questions are very provocative, as his questions always are. He asks whether it is possible that the spleen serves as a kind of reservoir—as sort of a surge tank, perhaps—to keep the portal pressure from getting too high, and suggests that perhaps if the spleen were removed, bleeding would be more likely to occur. I know of no evidence for or against this, but it seems a reasonable possibility. However, if a shunt is established and is satisfactory, this objection to removing the spleen in the course of treatment of portal congestion should be obviated. I cannot answer his second question, about the chance of arteriovenous anastomoses being present. It is a very interesting idea, and one that needs more work done on it.

Cirrhosis with Hemorrhage

FREDERIC W. TAYLOR, M.D., and JOE G. JONTZ, M.D., Indianapolis

It has been emphasized repeatedly that the immediate death rate is extremely high in cirrhotic patients having massive esophageal hemorrhage (Refs. 3, 8, 11, 13, 15, 18, 21, 24, 27). Therefore, to repeat this assertion with still another review of cases would seem superfluous. However, it is our opinion that the story has only half been told—that in the light of present surgical attempts to control the situation, the entire implication is not fully appreciated—and that the assertions of surgical triumphs over this condition should be tempered with some of the thoughts here expressed.

This review was originally undertaken to evaluate our results in the treatment of hemorrhaging cirrhotic patients. We could not believe our experiences were as bad as those of others. The review proved to be a monotonous repetition of what had already been reported. It indicated an unbelievably high mortality immediately following the first massive hemorrhage, with half the patients dead at two months. After this the disease leveled off, with an acceptable death rate. Though other reports may indicate minor variations, there is an astoundingly uniform pattern to all survival curves in this group of patients.

Material

The cases studied were those of 445 patients who entered the Indianapolis Veterans Administration Hospital during the 10-year period 1946-1956 with the diagnosis of cirrhosis. One hundred twenty-seven of these were dropped from the study because it was thought that laboratory and clinical findings did not warrant the diagnosis. This number included 27 patients who were subsequently shown at autopsy to have hepatitis, metastatic liver carcinoma, cardiac failure, or hemachromatosis.

Among the remaining 318 patients were 102 who had massive bleeding. The term massive bleeding is obviously difficult to define. Here it is used to include those patients requiring at least two blood transfusions because of acute blood loss. This is not an infallible division of cases but seems fairly sound. It is fully admitted that any definition other than that based on circulating blood volume is subject to criticism.

The diagnosis of cirrhosis was confirmed by autopsy or biopsy in 79 of the bleeding group. The basis of cirrhosis was alcohol, or at least an association of alcohol, in nearly 90%. A few gave a definite history of severe hepatitis. One patient was included who had a normal liver but was typical of portal hypertension, with varices and portal pressure of 35 cm. of saline.

Diagnosis in the 216 nonbleeding cirrhotic patients was established largely by clinical and laboratory findings. The diagnosis was confirmed by tissue study in only 35. It is likely that a few of the nonbleeding cirrhotic patients actually had hepatitis, or that a few of the patients dropped from the study actually had cirrhosis rather than hepatitis. This number must be very small and cannot alter our conclusions. In this particular study the "nonbleeders" formed a rather rough control picture of cirrhosis as seen by us.

By and large, the patients were all treated symptomatically. The earlier patients of both groups were fed large quantities of protein when this was possible. During the last few years patients were given only normal amounts of protein, high carbohydrate, and low fat. We found no difference in the effects of these diets but feel that the latter is more nearly correct from a theoretical standpoint.

The massive bleeders received repeated blood transfusions, and attempts were made to control the immediate hemorrhage with gastric and esophageal balloons. Only 14 of these massive bleeders were operated upon. They received a variety of operations, from ligations to shunts. The number of surgical procedures was small, partly because we share a skepticism of surgery voiced by others.[6,9,25,28] There were seven hospital deaths in the patients treated surgically—all of desperately

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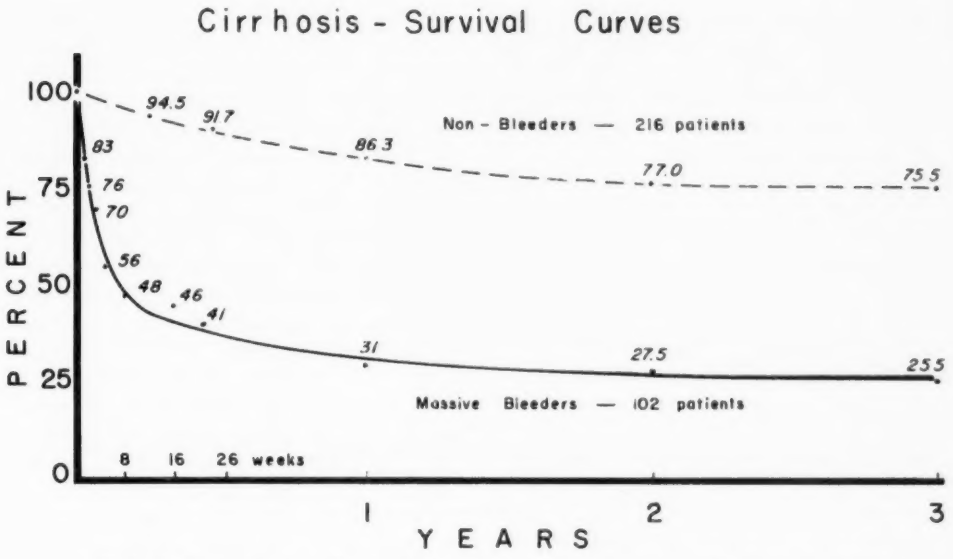

Cirrhosis survival curves. Survival after onset of first massive hemorrhage compared with the survival of those who have not bled. Operative portal shunts are normally performed on patients reaching the flat part of the lower curve; therefore surgical results must be compared with that normal expectancy, and not with "70% dead in a year."

ill patients. Those who survived operation seemed to follow an unaltered course, being neither helped nor hurt by the experience. When all operative cases were omitted from the series, the resulting survival curve remained unchanged, with the same salient features. Therefore, these were not omitted from the summation.

Results

The over-all survival rate of hemorrhaging cirrhotic patients is graphically shown in the Figure. As previously noted, with only minor deviations, this is the same picture shown by others. It represents the present-day survival for this disease, with nearly one-half dead at four weeks following the first massive hemorrhage. After this early heavy toll, the survival curve flattens to approach that of the nonbleeding cirrhotic group. Our survival rate beyond the three-year period gave much the same flat curve. However, the follow-up in our itinerant patients was not satisfactory at the five- to seven-year stage. Therefore, the graph was not continued beyond three years.

Numerous studies and inquiries were made to determine the type of patient who hemorrhaged. This inquiry was unproductive, and no prognostications seemed valid. There was no general trend in blood study or blood chemistry which might indicate those patients who would bleed and those who would not. This seemed true also as to size of spleen, presence or absence of hypersplenism, and change in albumin-globulin ratio. Both bleeders and nonbleeders seemed to have experienced the same diseases, and the ages of the two groups were practically identical. Occasionally, the first suggestion that the patient might be suffering from cirrhosis was esophageal bleeding.

The hemorrhage itself often stood out as an inevitable and unalterable event. For instance, 25 patients had their first massive hemorrhage in the hospital after admission for other symptoms of cirrhosis. Of these, 23 died during that admission. There were 46 patients who died after their first massive hemorrhage (onset within two weeks of final admission to the hospital).

The association of hemorrhage and cholemic death has frequently been noted in this group of patients. The two (hemor-

rhage and coma) cannot be separated. Coma is so commonly dependent upon hemorrhage and brought about by hemorrhage that the two are unalterably linked together. To prevent massive hemorrhage is to prevent or delay impending cholemic coma.

There are those who assert that terminal cholemia is largely the result of elevated blood ammonia and that this elevation results from the inability of an abnormal liver to utilize the excessive ammonia brought from the disintegrating blood in the bowel. This may in part be true, though its importance has certainly been overemphasized. A far more logical mechanism would seem to be the inevitable complete liver failure which has been shown to follow a sustained hypotension.[12,22,23] We have never seen the cholemia of hemorrhage occur in patients who have not also had a sustained hypotension. Often the duration of this hypotension was well beyond the point at which irreversible damage might be produced in the liver. This mechanism must be even more critical to a liver that is already decompensated.

Surgery

Much has been written recently about the operative salvage of this group of cirrhotic patients with massive hemorrhage.[2-16,28] The enthusiasts point an accusing finger at statistics indicating that "half die two months after hemorrhage" or that "70% are dead in a year." Those who advocate some sort of portal-vein shunt contrast these figures with their own operative mortality of 10% or 15%. It is with this particular argument that we wish to take issue.

Two different groups of patients are being compared. First is the group which contains the immediate high mortality following the initial hemorrhage—"half die in two months." Those who advocate portal shunts have repeatedly warned against operation in these early cases. Patients who have jaundice, ascites, and albumin levels below 3 gm. are generally conceded *not* to be candidates for shunt operations. The risk is prohibitive. It is advised that these patients be treated medically until their condition can tolerate an operation. This delay allows enough time to pass that the patient who survives reaches the second group.

The second group might roughly be considered as those patients who did not die during the first two or three months following hemorrhage. This automatically places the patient in a comparatively favorable group with an acceptable mortality whether he has an operation or not. If a shunt is performed at this stage, complete credit is given to the operation and the results compared with the high mortality of the first group.

This is illustrated in the Figure. It is readily seen that the survival curve is quite respectable at a point two or three months after the initial massive hemorrhage. In fact, it very closely follows the pattern of that found in the nonbleeding cirrhotic group. Those who cite operative-shunt mortality figures must compare them with the flat survival curve as indicated after the first two or three months. Their results cannot be classed with the first portion of that curve, where "half die during the first two months." This particular feature has been strongly emphasized by Child,[4] in a comprehensive monograph, and inferred by Hallenback and Shocket.[14] Since the present article was first drafted, others have voiced the same skepticism. Cohn and Blaisdell[6] report an 86% mortality following the first massive hemorrhage, and Nachlas,[19] with a broad review of the literature, questions the whole idea of portal shunts. Nevertheless, the medical profession as a whole is not cognizant of these facts and continues to compare the low operative-shunt mortality with "70% dead" if not operated on.

It must be understood that we believe portal shunts are occasionally indicated, particularly in the chronic esophageal bleeders. The operation, however, is a very inefficient means of regulating excessive portal pressure.[26] Furthermore, it is disastrous to use in the very group where most lives are lost—that of the early acute case.

One cause of this failure may be that if a shunt is at all effective, it lowers the effective portal venous pressure and hence diminishes blood flow through the liver. With a decompensated liver this might be sufficient to spell disaster.

Numerous procedures have been suggested in attempts to rectify these operative deficiencies. O'Sullivan and Payne[20] have advocated the portacaval shunt as an emergency measure. Their suggestion might be questioned, since only two of their nine patients were operated upon less than one month after the original hemorrhage. Our own operative experience with jaundice and with liver decompensation has been disastrous.

Others have advocated ligation of the intraesophageal varices in the emergency of acute massive hemorrhage. The reports of Linton[17] are quite glowing. Our own results with intraesophageal ligations are much like those of Crile,[7] and have not been very encouraging in patients desperately ill with hepatic decompensation. We have had no experience with prophylactic surgery before the patient has bled.[27]

All this leads to the realization that little gain has been made against the disease. We are only surgically effective when the real fire has spent itself, with a heavy toll, leaving a few smoldering cases for operations. In many of these, any type of operation might do just as well as the definitive procedure for which so much is claimed. Improved treatment must be directed against the first few weeks of bleeding to produce effective salvage. The more one reviews and studies these cases the more one realizes how small a part surgery now plays in the over-all picture. Its applications are indeed limited.

There can be no doubt that abstinence of alcohol is the most important single factor in the management of most cirrhotic patients. Many good long-term operative results are dependent not so much upon the surgeon as upon whether or not the patient continues drinking. Beyond this we cannot go, since we know so little about the actual production of cirrhosis by alcohol. For that matter, the cause of esophageal varices and portal hypertension by cirrhosis is still a mystery.

Summary

A study was made of 318 patients with cirrhosis. From the laboratory and clinical records, we were unable to predict which patients would bleed from esophageal varices and which would not.

Our survival figures on patients following massive hemorrhage are identical with other reports. There is an unbelievably high early mortality rate, which so far has not been improved by surgery.

After the early heavy death toll from hemorrhage, these patients have an acceptable survival rate. Since definitive operations are performed during this low-mortality period, these results should be compared with normal life expectancy of *that* time, and not with "half dead at two months." Patients upon whom portacaval shunts have been performed are a highly selected group, by virture of having survived the ravages of the first or second massive hemorrhage.

Any great progress against the bleeding phase of this disease must be directed against its tremendous early mortality. The present limitations of surgery are fully admitted.

Hume-Mansur Building.

REFERENCES

1. Anlyan, W. G.; Shingleton, W. W.; Benson, W. R.; Stephen, C. R.; Salem, M., and Taylor, H. M.: A Study of Liver Damage Following Induced Hypotension, Surgery 36:375, 1954.

2. Blakemore, A. H.: Portacaval Shunting for Portal Hypertension, Surg. Gynec. & Obst. 94: 443, 1952.

3. Cates, H. B.: Surgical Treatment for Cirrhosis: Prognosis Subsequent to Omentopexy, Arch. Int. Med. 71:183, 1943.

4. Child, C. G., III: The Portal Circulation, New England J. Med. 252:837, 1955.

5. Cohn, R.: A Skeptical Evaluation of Portacaval Anastomosis for Gastrointestinal Hemorrhage in Cirrhosis of the Liver, Stanford M. Bull. 9:231, 1951.

6. Cohn, R., and Blaisdell, F. W.: The Natural History of the Patient with Cirrhosis of the Liver with Esophageal Varices Following the First Massive Hemorrhage, Surg. Gynec. & Obst. 106:699, 1958.

7. Crile, G., Jr.: Transesophageal Ligation of Bleeding Esophageal Varices, Surgery 42:583, 1957.

8. Douglass, B. E., and Snell, A. M.: Portal Cirrhosis: An Analysis of 444 Cases with Notes on Modern Methods of Treatment, Gastroenterology 15:407, 1950.

9. Dye, W. S.; Capps, R. B.; Baker, L. A.; Grove, W. J., and Julian, O. C.: Evaluation of Venous Shunt Surgery in Portal Hypertension, A. M. A. Arch. Surg. 74:959, 1957.

10. Ebeling, W. C.; Bunker, J. P.; Ellis, D. S.; French, A. B.; Linton, R. R., and Jones, C. M.: Management of Patients with Portal Hypertension Undergoing Venous-Shunt Surgery, New England J. Med. 254:141, 1956.

11. Fagin, I. D., and Thompson, F. M.: Cirrhosis of the Liver: An Analysis of 71 Cases, Ann. Int. Med. 21:285, 1944.

12. Fine, J.; Frank, H. A., and Seligman, A. M.: Traumatic Shock Incurable by Volume Replacement Therapy: A Summary of Further Studies Including Observations on the Hemodynamics, Intermediary Metabolism and Therapeutics of Shock, Ann. Surg. 122:652, 1945.

13. Fleming, R. G., and Snell, A. M.: Portal Cirrhosis with Ascites: An Analysis of 200 Cases with Special Reference to Prognosis and Treatment, Am. J. Digest. Dis. 9:115, 1942.

14. Hallenbeck, G. A., and Shocket, E.: An Evaluation of Portacaval Shunts for Portal Hypertension, Surg. Gynec. & Obst. 105:49, 1957.

15. Hendrikson, E. C.: Cirrhosis of the Liver, with Special Reference to Surgical Aspects, Arch. Surg. 32:413, 1936.

16. Linton, R. R.: The Emergency and Definitive Treatment of Bleeding Esophageal Varices, Gastroenterology 24:1, 1953.

17. Linton, R. R., and Ellis, D. S.: Emergency and Definitive Treatment of Bleeding Esophageal Varices, J. A. M. A. 160:1017, 1956.

18. Nachlas, N. M.; O'Neil, J. E., and Campbell, A. J. A.: The Life History of Patients with Cirrhosis of the Liver and Bleeding Esophageal Varices, Ann. Surg. 141:10, 1955.

19. Nachlas, M. M.: A Critical Evaluation of Venous Shunts for the Treatment of Cirrhotic Patients with Esophageal Varices, Ann. Surg. 148:169, 1958.

20. O'Sullivan, W. D., and Payne, M. A.: The Emergency Portacaval Shunt, Surg. Gynec. & Obst. 102:668, 1956.

21. Patek, A. J., Jr.; Post, J.; Ratnoff, O. D.; Mankin, H., and Hillman, R. W.: Dietary Treatment of Cirrhosis of the Liver, J. A. M. A. 138:543, 1948.

22. Raffucci, F. L., and Wangensteen, O. H.: Tolerance of Dogs to Occlusion of the Entire Afferent Vascular Inflow to Liver, S. Forum, p. 191, 1950.

23. Rappaport, A. M.; MacDonald, M. H., and Borowy, Z. J.: Hepatic Coma Following Ischemia of Liver, Surg. Gynec. & Obst. 97:748, 1953.

24. Ratnoff, O. D., and Patek, A. J., Jr.: The Natural History of Laennec's Cirrhosis of the Liver, Medicine 21:207, 1942.

25. Ripstein, C. B.: Experiences with Portacaval Anastomosis in the Treatment of Portal Hypertension, Surgery 34:570, 1953.

26. Taylor, F. W.: Portal Tension and Its Dependence on External Pressure, Ann. Surg. 140:652, 1954.

27. Welch, C. S.; Kiley, J. E.; Reeve, T. S.; Goodrich, E. O., and Welch, H. F.: Treatment of Bleeding from Portal Hypertension in Patients with Cirrhosis of the Liver, New England J. Med. 254:493, 1956.

28. Welch, C. S.: Management of Patients with Mass Hemorrhage from Esophageal Varices and Cirrhosis of the Liver, Surgery 41:1029, 1957.

Closed Chest Injury

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Observation of patients who have suffered ill effects from closed chest trauma reveals a characteristic pattern of injury. Of late, considerable interest and success in the treatment of certain lesions of this type involving the heart and great vessels have tended to enhance the significance of this pattern of injury. In this presentation, a few case reports will be briefly reviewed to emphasize the physiological reasons for their production, the rationale of their treatment, and their clinical pattern.

Most injuries of the chest are not isolated, and many are initially not considered of major significance. It is essential that the late manifestations or complications not be overlooked.

Several case reports of traumatic rupture of the heart with an intact chest wall have appeared since Kellert's initial presentation in 1917.[1] Because of the high pressures involved, survival is generally not expected in instances of ventricular rupture. In instances of atrial rupture alone, wherein the pressure is much lower, survival may occur. This expectation is confirmed by the findings of Parmley and his associates.[2] Their review of the necropsy records of 67 patients who suffered rupture of the right or left atrium showed that 19% survived the initial injury. In such instances the challenge to bring surgical benefit to these patients appears sound and feasible. Of interest is the reported survival of 20 patients who incurred traumatic ventricular septal defects.[3-9] Survival, except temporarily, among those who have incurred traumatic atrial septal defects has not been noted.

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Report of Cases

CASE 1.—Four passengers were injured when the automobile in which they were riding was involved in an accident. The two front-seat passengers suffered multiple bony injury but survived. One of the rear-seat passengers suffered a complete and fatal rupture of the aorta. The other passenger survived for 18 hours. He had associated severe injuries, and at autopsy a moderate contusion of the heart was noted, in the absence of chest-wall injury.

Injury to the venae cavae, with their low pressure, usually results in thrombosis and blockage. Aneurysm formation is not seen. Injury to the pulmonary artery, its pressure being within the medium range, may result in either aneurysm formation or obstruction.

CASE 2.—A young soldier complained only of mild hemoptysis following exposure to bursting explosives. There was no evidence of chest-wall injury. Routine x-ray examination of the chest several months later suggested abnormal findings, and angiocardiography demonstrated obstruction of the right pulmonary artery and superior vena cava.[10,11] Divided pulmonary function studies showed only a 20% oxygen uptake in the right lung. The patient was asymptomatic, and surgical exploration was not advised.

Injury to the aorta seems to have a predilection for the points where aortic fixation occurs, namely, the ascending aorta and the descending aorta opposite the ligamentum arteriosum.

Surgical excision and repair of traumatic aneurysms in the latter location are feasible. We have employed partial bypass technique (left atrium to left femoral artery).[12] Our recent experience has encouraged us to seek earlier attempts at repair. A review of 275 necropsy case records of aortic rupture available at the Armed Forces Institute of Pathology, showed that 15% of the patients

survived temporarily. This finding suggests the possibility of further extending the surgical efforts in this area.[13]

CASE 3.—A 21-year-old man sustained fractures of the left tibia, right radius, and a skull injury in an automobile accident in 1957. There was no evidence of chest-wall injury. In March, 1958, a routine chest roentgenogram revealed a widening of the mediastinal shadow, and aortography confirmed the presence of an aneurysm of the descending aorta. He soon underwent excision of the aneurysm and replacement with a Teflon graft, utilizing a partial left bypass of the heart. He is well and doing active military duty.

In young persons, the elastic chest wall may be so markedly compressed as to produce minute hemorrhages throughout both lung fields. With removal of the compressing force, the natural recoil of the chest wall causes it to resume its normal configuration, leaving little evidence of external injury. Severe dyspnea, cyanosis, and hemoptysis may occur. Rapid clinical and roentgenographic improvement occurs if survival can be achieved for the first few days.[14]

Vessels within the pulmonary parenchyma, in which the pressure is relatively low, may be torn. The result may be the production of a solitary intrapulmonary hematoma.[15] The initial chest injury may be considered trivial. The differential diagnosis may be difficult, particularly in the absence of recent chest roentgenography. Surgical exploration may be indicated if trauma cannot be established as the causative agent.

Disruption of the lung parenchyma itself without appreciable vessel or bronchial damage presents a still different pattern, namely, a spherical air-containing lung cavity.[16,17] Though the created defect may be small, the resultant cavity is of larger size than is accounted for by the actual lung destruction. This is attributed to the normal elastic lung pulling centrifugally. Cavity obliteration generally occurs, and if the traumatic nature can be established, a reasonable period of a few weeks should elapse to permit healing. If closure does not occur, surgical extirpation is advisable.

Bronchial injury may occur alone or in combination with other injuries, and should always be suspected. The auscultatory finding of a "mediastinal crunch" or the presence of subcutaneous emphysema is almost diagnostic. If the break is small, the lesion may be self-limiting. Rapid deterioration in the patient's condition may, however, become apparent after a bout of coughing. Further bronchial damage may result from the increased intrabronchial pressure.[18] Simultaneous rupture of the esophagus may occur, with the subsequent formation of a traumatic tracheoesophageal fistula.

CASE 4.—A young man suffered a fracture of the sternum in an automobile accident. Subcutaneous emphysema developed immediately, and a tracheotomy was done. Subsequently, a traumatic tracheoesophageal fistula was successfully repaired, and the patient is well.

Rupture of the diaphragm occasionally follows closed chest injury. Although early surgical repair is indicated, the nature of the injury may go unnoticed. Here, again, a brief follow-up period, including chest roentgenography, should be accomplished after apparently initial recovery.

Summary

Severe intrathoracic injury may follow mild trauma to the chest wall. Certain features of cardiac injuries, which present a challenge and hope for successful surgical therapy, are discussed. Emphasis is placed on the patterns of production of closed chest injuries. Compression of the thoracic cage, pulmonary hematoma, traumatic lung cavitation, rupture of the tracheobronchial tree, and large-vessel injury with aneurysm formation and obstruction are briefly reviewed. It is felt that an immediate awareness of these and similar conditions will increase the acute, as well as late, salvage rates following closed chest injury.

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REFERENCES

1. Kellert, E.: Traumatic Rupture of the Heart: Report of a Case with Uninjured Chest Wall, J. Lab. & Clin. Med. 2:726, 1917.

2. Parmley, L. F.; Manion, W. C., and Mattingly, T. W.: Nonpenetrating Traumatic Injury of the Heart, Circulation 18:371, 1958.

3. Pierce, C.: Data to be published.

4. Lillehei, C. W., cited by Cary and others.[5]

5. Cary, F. H.; Hurst, J. W., and Arentzen, W. R.: Acquired Interventricular Septal Defect Secondary to Trauma: Report of 4 Cases, New England J. Med. 258:355, 1958.

6. Guilfoil, P. H., and Doyle, J. T.: Traumatic Cardiac Septal Defect: Report of a Case in Which the Diagnosis Is Established by Cardiac Catheterization, J. Thoracic Surg. 25:510, 1953.

7. De Witte, P. E.; Van Der Hanwaert, L. G., and Joossens, J. V.: Traumatic Rupture of the Interventricular Septum, Am. Heart J. 54:628, 1957.

8. Pollock, B. E.; Markelz, R. A., and Shuey, H. E.: Isolated Traumatic Rupture of the Interventricular Septum Due to Blunt Force, Am. Heart J. 43:273, 1952.

9. Paulin, C., and Rubin, I. L.: Complete Heart Block with Perforated Interventricular Septum Following Contusion of the Chest, Am. Heart J. 52:940, 1956.

10. Magidson, O., and Jacobson, G.: Thrombosis of the Main Pulmonary Arteries, Brit. Heart J. 17:207, 1955.

11. Robinson, G.; Glotzer, P.; Gilbert, M., and Hurwitt, E.: Aortic Homograft Replacement of the Main Pulmonary Artery, J. Thoracic Surg. 36:555, 1958.

12. Cooley, D. A.; De Bakey, M. E., and Morris, G. C., Jr.: Controlled Extracorporeal Circulation in Surgical Treatment of Aortic Aneurysms, Ann. Surg. 146:473, 1957.

13. Parmley, L. F.; Mattingly, T. W.; Manion, W. C., and Jahnke, E.: Nonpenetrating Traumatic Injury of the Aorta, Circulation 17:1086, 1958.

14. Forsee, J. H.; Blake, H. A., and Goyette, E. M.: Chest Clinics: "Closed Chest Injury," Surgery 40:763, 1956.

15. Salyer, J. M.; Blake, H. A., and Forsee, J. H.: Pulmonary Hematoma, J. Thoracic Surg. 25:336, 1953.

16. Moolton, S. F.: Mechanical Production of Cavities in Isolated Lungs, Arch. Path. 19:825, 1935.

17. Forsee, J. H., and Blake, H. A.: Recognition and Management of Closed Chest Trauma, S. Clin. North America 38:1545, 1958.

18. Mitchel, B. F., and Davis, M. V.: Closed Rupture of the Trachea, Am. Surgeon 24:223, 1958.

Is Appendicitis Decreasing in Frequency?

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For some time it has been known that the death rate from appendicitis has been decreasing. This decrease can be shown both at the local and at the national level, and is generally attributed to such factors as better surgery, the use of sulfonamides and antibiotics, a better understanding of fluid and electrolyte balance, improved anesthesia, the use of intestinal tubes, better diagnosis, and better education of the public regarding the disease, its early symptoms, the dangers of laxatives, etc.

The National Office of Vital Statistics of the Department of Health, Education, and Welfare[1] reports that the death rate for appendicitis in this country dropped from 8.1 per 100,000 population in 1941 (10,789 deaths) to 1.3 per 100,000 in 1956 (2,103 deaths). Age-adjusted death rates for appendicitis among industrial policyholders of the Metropolitan Life Insurance Company dropped from 9.6 per 100,000 in 1939-1940 to 4.9 in 1944-1945, and 1.9 in 1949-1950.[2] Likewise, the crude death rates from appendicitis per 100,000 policyholders of Metropolitan Life Insurance Company dropped from 10.9 in 1911 to 10.2 in 1939, 5.8 in 1942, 3.4 in 1946, and 2.2 in 1949.[2]

According to a study made in the United States Navy,[3] the incidence of appendectomy rose from 1916 in a somewhat irregular fashion to reach a peak in 1935. It remained at a high plateau for several years and then began to decline gradually. In the earlier years the appendectomy rate was about 6 per 1,000 active personnel; it rose to a peak of 14, and then declined to a little over 4 per 1,000.

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Total death rates from all causes in the United States have also dropped, but the decrease is not as great as that from appendicitis. In 1941 the crude death rate was 10.5 per 1,000 per year,[4] whereas in 1956 the rate was 9.4 per 1,000.

These figures are not new and are well known to students of the disease. The big question that presents itself, then, is what accounts for the decrease? Is it due solely to better recognition and better treatment, or is it due in part at least to a real decrease in the incidence of the disease? The purpose of this paper is to attempt to answer these questions by gathering facts and figures from representative hospitals at both the local and the national level, and to note any change in the frequency of appendectomy for acute appendicitis in a 15-year period, and, more important, any changes in the number of proved cases of acute appendicitis in this period of time. Specifically, we have gathered statistics for the years 1941 and 1956. To do this, we have written to representative hospitals throughout the country for the following information:

1. Number of admissions or discharges for the years 1941 and 1956
2. Number of surgical procedures in the hospitals for the same years
3. Number of primary appendectomies in these same years
   (*a*) Number of cases of acute appendicitis proved pathologically wherever possible
   (*b*) Number of cases of nonacute appendicitis for the same years. Appendectomies done incidental to other operations, such as cholecystectomy, hysterectomy, etc., were not used.

Numerous difficulties have been encountered which have interfered somewhat with the thoroughness and completeness of the study. Some hospitals did not have the desired information, especially for 1941. In

some instances record-room methods and records were changed some time between 1941 and 1956, making records for the earlier date difficult or impossible to obtain. This was the case even in some large teaching hospitals. In other cases the records were available, but for local reasons the hospitals could not supply the requested information.

In the earliest phase of this study the incidence of acute appendicitis was studied in the Salt Lake City hospitals. When it appeared that there was a substantial reduction in the number of acute appendices removed, it was decided to expand the study. In the next phase a group of large metropolitan, usually university or teaching hospitals were studied. It soon became apparent that there was a substantial decrease not only in the ratio of appendectomies to other surgical procedures but in the actual number of acute appendices removed, despite in most cases a great increase in the number of hospital admissions and the number of surgical procedures done. The question then arose whether this decrease could be due to the greater incidence of appendicitis in suburban or rural hospitals. In other words, are more acute appendices now being removed in the latter group of hospitals, which at the earlier date, 1941, were being sent to the

TABLE 1.—*Metropolitan Hospitals*

Hospitals	Admissions		Surgical Cases		Primary App.		Acute App.		Nonacute App.	
	1941	1956	1941	1956	1941	1956	1941	1956	1941	1956
Swedish Seattle	7,994	16,529	5,599	9,915	219	153	165	149	54	4
University of Pennsylvania Philadelphia	11,063	23,709	9,697	19,898	305	165	179	148	126	17
University of Louisville Louisville	11,953	10,211	5,418	4,445	158	49	123	33	35	16
Los Angeles County Los Angeles	49,376	87,314	16,070	26,058	1,479	721	1,141	510	338	211
University of Minnesota Hosps. Minneapolis	9,159	14,028		8,785	168	48	110	40	58	8
St. Mark's Salt Lake City	4,681	12,436	2,791	5,609	425	286	256	193	169	93
Hermann Houston, Texas	4,713	27,553	2,852	14,249	269	392	83	258	186	134
Veterans Administration Hines, Ill.	9,825	20,889	5,387	10,723	86	71	60	56	26	15
Holy Cross Salt Lake City	5,136	9,421	2,526	4,954	503	100	258	73	245	27
Latter-Day Saints Salt Lake City	9,639	18,573	4,950	18,589	1,147	308		232		76
Hospital of Good Samaritan Los Angeles	10,511	16,496	8,133	11,330	310	144	210	94	100	50
University Hospitals of Cleveland Cleveland	18,559	23,299	10,956	14,533	257	161	208	155	49	6
Methodist Peoria, Ill.	7,226	16,099	1,037	2,205	412	424	290	317	122	107
St. John's Springfield, Ill.	13,697	21,673	6,719	11,716	366	171	206	147	160	24
Evangelical Deaconess St. Louis	7,889	10,045	3,998 (1948)	4,002	353 (1948)	113	164 (1948)	75	189 (1948)	38
Barnes St. Louis	14,157	28,734	9,590 (1943)	19,963	237	209	121	115	116	94
Memorial Springfield, Ill.	3,948	9,918	1,924	3,905	211	153	85	94	126	59
Madison General Madison, Wis.	6,403	13,316	4,526	8,076	269	193	135	143	134	50
University Hospitals Madison, Wis.	13,098	13,643	4,621	5,450	214	59	75	46	62	13
Totals	219,027	393,896	106,794	204,405	7,388	3,920	3,869	2,878	2,295	1,042

TABLE 2.—*Rural, Suburban, and "Smaller-City" Hospitals*

Hospitals	Admissions		Surgical Cases		Primary App.		Acute App.		Nonacute App.	
	1941	1956	1941	1956	1941	1956	1941	1956	1941	1956
Hughes Memorial Spanish Fork, Utah	188	695	32	306	20	24				
Logan Hospital of Latter-day Saints Logan, Utah	3,929 (1950)	3,620	2,245 (1950)	1,730	189 (1950)	119	153 (1950)	97	36 (1950)	22
Marshall Browning Du Quoin, Ill.	950	2,487	784	848	112	50	77	34	35	16
Utah Valley Provo, Utah	2,450 (1946)	7,084	941 (1946)	3,130	153 (1946)	181				
Iron County Cedar City, Utah	964 (1939)	1,545	350 (1939)	469		57	129 (1939)	41		26
Henrotin Chicago, Ill.	2,882	3,286	973	1,498	51	24	48	19	3	5
St. Joseph's St. Charles, Ill.	1,861	6,623	537	835	134	99	63	83	71	16
St. Mary's Cottonwood, Idaho	558 (1942)	1,172	192 (1942)	206	44 (1942)	20				
St. Luke's Boise, Idaho	5,967	7,117	2,768	3,728	167	101		69		32
St. Elizabeth Danville, Ill.	4,051	9,310	1,705	3,220	281	155	241	122	40	33
Highland Park Highland Park, Ill.	1,475	4,923	710	1,835	95	90	66	72	29	18
St. Mary's Oshkosh, Wis.	4,484	9,189	1,940	2,929	201	131	182	124	19	7
Mercy Benton Harbor, Mich.	2,625	6,419	1,552	2,320	313	80	115	54	198	26
Oneida County Malad City, Idaho	302	524	133	122	51	13				
Providence Wallace, Idaho	1,392	2,264	330	440	37	26	15	5	22	21
St. Francis Cape Girardeau, Mo.	2,928	4,965	1,113	2,651	265	70	137	43	128	27
Caribou County Soda Springs, Idaho	940	1,228	456	218	122	62				
St. Alphonsus Boise, Idaho	3,212 (1948)	7,113	2,020 (1948)	3,219	331 (1948)	90	233 (1948)	68	98 (1948)	22
St. Luke's Boise, Idaho	5,967	7,117	2,768	3,728	167	101		69		32
Memorial Hosp. of Du Page County Elmhurst, Ill.	3,762	13,167	1,803	5,796	241	259	109	145	132	114
Totals	50,887	99,848	23,352	39,228	2,974	1,752				

metropolitan hospitals? As the third phase of the study, then, a group of small, rural, and suburban hospitals were studied in the same way and compared with the metropolitan group.

Results

Totals for 19 metropolitan hospitals are as follows: admissions, 211,138 for 1941 and 383,841 for 1956; surgical procedures, 106,794 for 1941 and 204,405 for 1956; primary appendectomies, 7,388 for 1941 and 3,920 for 1956; acute appendices removed, 3,869 for 1941 and 2,878 for 1956; nonacute appendices removed, 2,295 in 1941 and 1,042 in 1956.

In several of the small rural hospitals it was impossible to obtain a breakdown of the primary appendectomies into removals of acute and removals of nonacute appendices, since no pathology reports were available. We have had, therefore, to eliminate these hospitals in the totals for acute and nonacute appendices but have retained them in the Table for the other figures, including primary appendectomies. The totals for 20 hospitals in this category, ignoring the breakdown of the figures for primary ap-

pendectomies into those for acute and those for nonacute appendices, are as follows: Admissions were 50,887 for 1941 and 99,848 for 1956; surgical procedures were 23,352 in 1941 and 39,228 in 1956, and 2,974 primary appendectomies were performed in 1941 and 1,752 were performed in 1956. The totals for the hospitals in this rural, suburban, and "smaller-city" group in which the figures are completed with a breakdown into acute and nonacute appendices give the following figures (for 12 hospitals): Admissions were 33,551 in 1941 and 73,366 in 1956; surgical procedures were 15,712 in 1941 and 27,321 in 1956; primary appendectomies were 2,250 in 1941 and 1,193 in 1956; acute appendices were 1,439 in 1941 and 866 in 1956; nonacute appendices were 811 in 1941 and 327 in 1956.

Incidentally, the figures from about 30 hospitals had to be discarded completely because of incomplete and unsatisfactory reports.

From a study of the totals of these two groups of hospitals, it becomes clear that the rather striking decrease in the incidence of acute appendicitis in the metropolitan group of hospitals is also found in about the same degree in this group of rural and small hospitals. It appears to us that this is strong evidence that the decrease in this incidence in the metropolitan hospitals is not accounted for by a tendency for patients to have their acute appendices removed nearer home, rather than go into the larger cities for their operation.

An interesting side-light of this study is the great decrease in the number of primary appendectomies for nonacute appendicitis. This speaks well for better diagnostic studies and better surgical judgment and may well be attributed, in part at least, to the activities of the Joint Committee on Accreditation, Tissue Committees, etc.

Another interesting by-product of the study is the great drop in the ratio of appendectomies to the total number of surgical procedures in the hospitals. Undoubtedly, this decrease is due far more to the great increase in the frequency of other types of surgery—not only newer operations in general surgery but also a great increase in neurosurgery, orthopedics, plastic work, etc., than it is to the actual decrease in the frequency of primary appendectomy. For example, at the Holy Cross Hospital in Salt Lake City in 1941 primary appendectomies constituted 22% of all surgical procedures, and half of these, or 10% of all surgery done, were for acute appendicitis. In 1956, only 2% of all operations were primary appendectomies, and 1.4% of the total was for acute appendicitis. At the Latter-day Saints Hospital in Salt Lake City the figures are virtually identical and in 1941 at St. Mark's Hospital in Salt Lake City, 13% of all operations were primary appendectomies and 9% were for acute appendicitis, while in 1956 these figures were 5% and 3%, respectively.

The only other study of this type which we have been able to find is one by Bothe,[3] in Philadelphia. Recently he reported a study of the Philadelphia area for a 10-year period between 1944 and 1953. In 17 Philadelphia hospitals he found 4,574 operations for acute appendicitis in 1944 and 1,889 in 1953, despite a considerable increase in the bed capacity of these institutions. In other words, only 37% as many operations were done in Philadelphia hospitals for acute appendicitis in 1953 as in 1944. He also extended his studies to the rural and suburban hospitals in the Philadelphia area and again found a comparable decrease.

What are the etiological factors in this apparent decline in appendicitis? Many possible explanations present themselves; yet none of them seems very satisfying. One of these is the possible effects of antibiotics. Although some cases of appendicitis seem to follow an upper respiratory or gastrointestinal infection, these cases are in the minority; and even if antibiotics and sulfonamides were given for these antecedent diseases, it is uncertain whether they would reduce the likelihood of appendicitis following them. However, the great ma-

jority of cases of appendicitis are not preceded by an antecedent disease, and it is highly unlikely that many of these patients have been getting these drugs for any reason in the immediate period before the onset of the disease. It is conceivable, of course, that these patients have had antibiotics in the remote past and that these may have had some influence. Another possible factor is diet. Are we better nourished, less likely to be deficient in vitamins and minerals and other essential food elements? There is no doubt that our dietary habits and nutrition have improved in the past couple of decades, due to a better understanding of nutrition and the availability of a greater variety of foods. However, there is no proof of the relationship of these possible factors to this problem, and when one considers the fact that in many less civilized peoples, with limited foods and vitamin intake and less satisfactory nutrition, the disease is much less frequent than it is in this country, the influence of diet would seem to be of very doubtful significance.

Summary

There is strong evidence that in the past 15 years there has been a decrease in the incidence of acute appendicitis. Although it has been known for some years that the mortality rate from appendicitis has been decreasing, it has been assumed that this is due to the use of antibiotics, better diagnosis, expert anesthesia, the use of blood and other fluids, etc. It now appears that part of this decreased mortality is due to a decreasing incidence of the disease. This decrease is not accounted for by a more critical diagnostic approach to the disease, as fostered by the hospital tissue committees, for not only has the incidence of appendectomy decreased but the actual number of proved cases of acute appendicitis has substantially decreased as well. Moreover, the apparent decreased incidence of the disease and the decreased frequency of appendectomy are apparently not due to an increased frequency of the operation in the suburban and rural hospitals, as shown by these studies.

It is interesting to note the great change in the ratio of appendectomies to the total number of surgical cases in a hospital. Whereas appendectomy in 1941 made up about 10% of all surgical procedures, it now constitutes only about 2%. This change is probably due only partially to the decreasing incidence of appendectomy. Most of it is more likely due to the greatly increased frequency of other and newer types of surgery which have been introduced in this period.

The cause of the apparent decreasing frequency of the disease is not clear. Better nutrition, better dietary habits, and the widespread use of sulfonamides and antibiotics as possible preventive measures are some of the possible factors which come to mind, but we know of no scientific evidence that these are responsible. It is conceivable that the whole picture is simply one of cyclical decrease, as is seen in some other diseases which increase and decrease in cyclical manner without apparent cause. The whole problem is a rather provocative one.

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REFERENCES

1. Vital Statistics of the United States, Public Health Service, Vol. 48, No. 4, U. S. Department of Health, Education, and Welfare, National Office of Vital Statistics, May 6, 1958.

2. Statistical Bulletin, Health and Longevity at the Mid-Century, Metropolitan Life Insurance Company, Vol. 31, 1950-1951, p. 31.

3. Collins, S. D.: Surgical Experience in Selected Areas of the United States, Public Health Service, Monograph No. 38, Department of Health, Education, and Welfare, 1956.

4. Vital Statistics Special Report, Public Health Service Vol. 48, No. 10, U. S. Department of Health, Education, and Welfare, National Office of Vital Statistics, Sept. 4, 1958, Table I.

5. Bothe, F. A.: Appendectomy, S. Clin. North America, pp. 1615-1623, Dec., 1957.

DISCUSSION

DR. LOUIS T. PALUMBO, Des Moines, Iowa: Drs. Castleton, Puestow, and Sauer deserve a great deal of credit for their astute observation of this interesting problem, which may represent a national trend. Further studies by others in this organization may help to crystallize the reason for this change. Our studies very much parallel their report. During the past 12 fiscal years, 1947-1958, a total of 1,823 appendectomies were performed at the Veterans hospital in Des Moines. Of this number, 1,600 were for acute appendicitis; 1,194 were performed as an emergency procedure, beyond the regular daily operative schedule. There were four postoperative deaths, representing a 0.2% mortality. There have been no deaths since 1953, in 439 appendectomies. Even though there has been a fairly stable work load during this period, the incidence of appendicitis and the number of appendectomies performed have shown a steady decline since 1947 (Fig. 1). For example, in 1947 the incidence of appendicitis in 3,000 patients treated on the surgical service was 6.4%; in 1958, it was 2.6%. For the same period, the number of appendectomies performed, as compared with the total operations performed, revealed a significant decrease; 15.3% of all procedures were appendectomies, as compared with 6.3% of the total operations performed in 1958 (Fig. 2). This progressive decline has also been reflected in the number of emergency appendectomies performed; 10.7% of all surgical operations performed in 1947 were for acute appendicitis, whereas in 1958 only 3.9% of the total were for this acute disease (Fig. 2). It is difficult to account for this significant reduction in the incidence of appendicitis among our population. The age incidence, work load, and total surgical procedures performed have remained fairly stable during the last six years of this study (Fig. 2). Even though there has been a significant decrease in the admission rate for appendicitis and the number of appendectomies performed, from a peak of 252 in 1948 to a low of 58 in 1957, the total patient load and operative procedures performed have increased or remained constant (Fig. 2). In other words, other surgical conditions have increased to maintain the work load equivalent to or above that created by the hiatus of 150-180 patients formerly treated annually for appendicitis.

With no change in the type of patients admitted to our Center, it is difficult to assume that there has been a diffusion of these acute cases to other hospitals, either locally or in smaller

Fig. 1.—Patient and major surgical work loads for 12-year period. In spite of a constant work load for the last six years, the number of appendectomies performed shows a continuous downward trend.

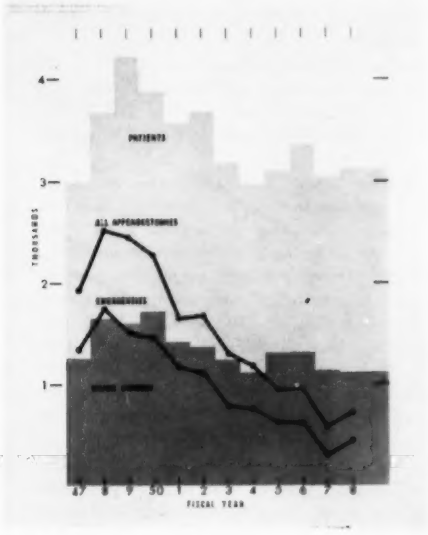
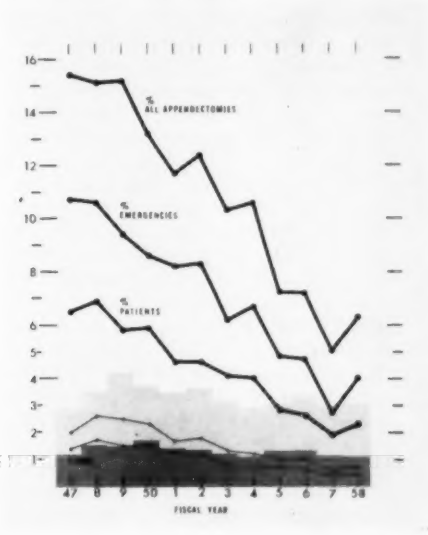


Fig. 2.—The incidence of appendicitis and appendectomies performed, calculated on a percentage basis, against the total work load is shown. A progressive downward trend in all categories is noted in the 12-year period.



communities. The significant and progressive decline apparently is due to other causes, or may be in some way connected with the many favorable features which accompany a better national economy.

DR. DEAN SAUER, St. Louis: We who have collaborated with Dr. Castleton have done so in a very minor measure, and I should like to be the first to say that I am keenly aware of his prodigious effort in the acquisition, the compilation, the sorting, and the interpretation of the multiple data which came across his desk. I know he would not mind my reemphasizing one statistic in the slides as they were shown, namely, the fact that between 1911 and 1939, in that 28-year period, the accrued death rate from appendicitis decreased from 10.9 per 100,000 to but 10.7 per 100,000, indicating that in a 28-year period the mortality rate, the accrued death rate from appendicitis, decreased only 0.2%. However, in the period from 1939 to 1942 that accrued death rate was decreased from 10.7% to 5%. Progressively, it was halved each year until about 1956, suggesting to me, at least, that at about 1939 something occurred to lessen this death rate.

I should like to postulate the advent of the chemotherapeutic agents, and in their wake shortly the antibiotics, not so much on the basis that they were used in the treatment of appendicitis, and therefore aborted the disease, but, rather, that their national and international use perhaps has done something to a specific strain of organisms which might ordinarily have been thought to incite appendicitis in the first place.

I know we have not thought of any specificity in an organism or a group of organisms in the production of appendicitis, but the thought occurs to me that perhaps there is some organism or group of organisms which tends to initiate the disease, and that this entire group of bacteria has been changed as the organisms have been passed from one individual through another, and therefore might not be existent at the present time. It makes interesting speculation.

There is also suggested a rather natural and simple clinical study, which might be carried out. One might study the organisms, culturing them and subculturing them as they occur in the appendix in acute appendicitis, and also one might culture organisms from appendices which are removed incidentally at operation, being sure that the cultures are obtained from the appendix alone, and not from other areas of the intestinal tract, to see whether there is some specificity in the organisms initiating this disease.

DR. CHARLES B. PUESTOW, Chicago: Dr. Brown, may I rise also to give credit to Dr. Castleton for the tremendous amount of work that he did on this paper? I only helped to assemble some of the data and discussed the study a little with him.

He mentioned antibiotics in the treatment of the disease. I think their use can be ruled out to some degree as a cause of this decrease in appendicitis, as shown in Dr. Palumbo's discussion. Our patients at Hines come to the hospital when they are sick, and often are not treated with antibiotics at home by family doctors, and yet the incidence of the disease itself has declined at about the same rate as the operations.

The acute appendix, I am sure, is taken out by most surgeons without fear of the Tissue Committee. There was some decline of nonacute appendectomies, and some of that may have been induced by fear of having to appear before a Tissue Committee; but that decline is proportionately about the same as the decline in acute appendicitis itself. I think Dr. Castleton has done a very good job.

DR. PHILIP B. PRICE, Salt Lake City: Since we are engaging in speculation as to the reasons why we have this difference in incidence, I should like to present a somewhat different view, for what it may be worth. I had the opportunity of working for a good many years in China, at a university hospital, where we were interested in a difference between two groups of people existing simultaneously in the country. Among the rural people and common people in cities, appendicitis was extremely uncommon. On the other hand, among the student group and the people who lived in the ports, such as Shanghai or Tientsin, appendicitis was not uncommon at all, and the numbers even approached those we had seen over here. This observation was before the days of antibiotics; so they were not a factor. We speculated as to the reason for this contrast, and our best guess was the difference in diet. The group that included students and people from the ports in general had a much better diet, but it was a much more refined diet.

I should like to suggest that diet may be a factor that should not be thrown out too lightly in our present consideration. If I recall correctly—in coming back to this country after some years of absence one notices these things—the decrease in incidence of appendicitis coincided

fairly well with a general change in diet in this country, with increased use of roughage, or raw salads of various sorts, of whole-wheat bread, and that sort of thing—a much more diversified diet than was found previously.

DR. E. LEE STROHL, Chicago: I should like to commend Drs. Castleton, Puestow, and Sauer on this excellent study. I should like to tell you about the mortality rates that have been encountered with acute appendicitis, pathologically confirmed, at St. Luke's Hospital in Chicago. In 1938 the mortality rate was 3%. The number of appendectomies done annually, pathologically confirmed, was 287. In 1942, in the era of chemotherapeutic drugs, the mortality rate was 1.92%. The number of appendectomies done annually was less than 200. In 1947 the mortality rate was 1.48%, with 125 appendectomies done annually. In the last three years the mortality rate has remained approximately the same, namely, 0.6%. The number of acute appendices, pathologically confirmed, is less than 75 annually. However, the incidence of appendiceal abscesses is increasing. I should like to ask the essayists whether they will discuss why we are finding more appendices that go on to perforation than was the situation a few years ago.

DR. KENNETH B. CASTLETON, Salt Lake City: I am not sure than I can answer Dr. Strohl with certainty, but I cannot help feeling that we may be going too far in our efforts to avoid trouble with our tissue committees. I am aware of two cases in our hospital which were sent in for suspected appendicitis, but, because of some doubt in the minds of the physicians involved, operation was delayed for studies such as intravenous urography, colon x-rays, stool tests, and gynecological consultation. These cases went on to perforation before operation was carried out.

I would like to thank the discussants for their interest and valuable contributions, and, speaking for Drs. Puestow, Sauer, and myself, I want to thank the approximately 70 hospitals which were contacted during this study, and also the numerous doctors, several of whom are members of this organization, who helped so much in this study.

PRESIDENT BROWN: Dr. Balfour was here earlier and commended us very highly on the papers and the way in which they have been given. I think this last paper exemplifies a point of importance. It seems to me that Dr. Sauer might have brought in some reason for the reduction in numbers. He, as well as the rest of us at our hospital, know we have a slight amount of competition there, in which a man was said to make 1½ in. incision, a day and a half in the hospital, and $1.50 for the operation. There is also the true story about the Scotsman who came to this country and heard about the activities of American surgeons. On his identification card he wrote: "Note: I have already had my appendix removed twice."

Treatment of Acute Hemorrhagic Pancreatitis with Adrenocorticosteroids

Clinical and Experimental Observations

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A limited number of case reports have appeared in the literature which describe a beneficial response following the treatment of acute pancreatitis with adrenocorticosteroids.[4,6,9-13,16,19] The exact mechanism responsible for this improvement is not known; however, prevention of circulatory failure[5-7] and anti-inflammatory,[8,9,13,17] antienzymatic,[16] and antiallergic[13] effects have been suggested.

Included in the present study are two case reports of documented acute pancreatitis following abdominal operations. Both patients recovered after institution of adrenocorticosteroid therapy in conjunction with other supportive measures.

Report of Cases

CASE 1.—A 47-year-old white woman was hospitalized on July 28, 1954, with a four-week history of cramping right-sided abdominal pain, nausea, vomiting, and frequent eructations. Abnormal physical findings included a blood pressure of 210/110 and a firm, movable mass, 4 cm. in diameter, in the right midabdomen. Routine studies of blood and urine were within normal limits. Colon x-rays revealed a napkin-ring deformity in the right transverse colon.

A right hemicolectomy was performed on Aug. 5, for a carcinoma of the right transverse colon. On the second postoperative day, the patient complained of abdominal cramping, and examination revealed distention and exquisite tenderness. Her skin became cold, clammy, and slightly cyanotic, and relative hypotension (112/110) and tachycardia (110 beats per minute) developed. The leukocyte count was 25,000, hemoglobin 16 gm. % and hematocrit 44%. Acute pancreatitis was considered at this time; however, mesenteric venous thrombosis or some other abdominal emergency could not be ruled out. A preoperative blood amylase determination was not available. Reoperation revealed the abdomen to contain considerable serosanguineous fluid and obvious fat necrosis. The pancreas was edematous and hemorrhagic.

Prior to and during the 12 hours immediately following surgery, the patient received 1,000 cc. of whole blood, 900 cc. of plasma, 1,000 cc. of 5% dextrose in saline and 4,500 cc. of 5% dextrose in water, 800,000 units of penicillin, and 1 gm. of streptomycin. Intravenous hydrocortisone was started prior to surgery, when the patient's condition appeared to worsen, despite the rapid administration of fluids containing levarterenol (Levophed) bitartrate. A total of 200 mg. of hydrocortisone (intravenous) and 150 mg. of cortisone acetate (intramuscular) was given during the first 12-hour period. Within 24 hours an adequate blood pressure was maintained without vasoconstricting drugs. The dosage of intramuscular cortisone acetate (50 mg. every six hours) was gradually reduced and its administration discontinued on the fifth postoperative day. Intramuscular penicillin, 800,000 units, and streptomycin, 1.0 gm., were continued daily through the 12th postoperative day. Fluid and electrolytes were replaced on the basis of gastric suction and urinary losses. Oral alimentation was begun on the fifth postoperative day. Except for a fever, which subsided with spontaneous drainage of a wound abscess on the ninth postoperative day, the recovery was uneventful. She died three years later, with generalized carcinomatosis.

CASE 2.—A 56-year-old white woman was hospitalized on Feb. 21, 1957, because of vomiting and epigastric and right upper quadrant pain. The past history revealed several similar attacks. Complete gastrointestinal x-rays in December, 1956, were normal. Cholecystograms revealed a moderately distended gallbladder with no obvious calculi. Examination revealed exquisite tenderness in the epigastrium and subcostal areas. Laboratory determinations were normal except for serum amylase

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of 663 Somogyi units. The patient's symptoms subsided with conservative management, and on the fourth hospital day the serum amylase was 39.5 Somogyi units.

Laparotomy on Feb. 27 revealed an indurated pancreas and a distended, chronically inflamed gallbladder. A cholecystectomy was performed, and choledochotomy revealed stenosis of the sphincter of Oddi, which was treated by transduodenal sphincterotomy.

At 4 a. m. of the following day (approximately 12 hours after operation), the patient complained of severe epigastric pain, and her blood pressure was unobtainable. Administration of nasal oxygen and intravenous levarterenol bitartrate (4 cc. in 1,000 cc. of fluid) was followed by a prompt rise in blood pressure to 130/90. The hemoglobin was 17.6 gm. %, the hematocrit 53%, serum amylase 500 Somogyi units, and fasting blood sugar 185 mg. %.

During the next 24 hours, she received 200 mg. of hydrocortisone intravenously, and for the next week 50 mg. of intramuscular cortisone acetate every six hours. In addition, intravenous tetracycline (Achromycin), 1.0 gm., and intramuscular penicillin, 800,000 units, and streptomycin, 1.0 gm., were administered each day for one week. Initially, she received 100 cc. of salt-free serum albumin, and atropine, 0.04 mg., was given every four hours for one week. On the second postoperative day the amylase dropped to 239 units, and three days later, to 28 units. Thereafter she made an uneventful recovery.

Experimental Study

The multiplicity of therapeutic measures undertaken to control the shock and associated fluid and electrolyte imbalance in these cases makes an evaluation of any single agent difficult. Therefore, we have attempted to appraise the worth of adrenocorticosteroid therapy in a form of experimental pancreatitis, which we believe closely simulates the human disease, both in clinical course and in pathologic findings.

Methods and Materials

A total of 65 healthy mongrel dogs, with weights varying from 9 to 20.5 kg., were studied. The animals were fasted from 12 to 24 hours prior to operation and anesthetized with Veterinary Nembutal sodium* (25 mg. per kilogram of body weight). Using sterile techniques, the abdomen was opened through an upper abdominal midline incision. A polyethylene cannula was inserted directly into the opening of the large accessory pancreatic duct through a duodenotomy opening and secured in position with a silk ligature around the duct outside the duodenal wall (Fig. 1). The smaller pancreatic duct (Wirsung's) was ligated near its junction with the common bile duct. A 10 cc. mixture, consisting of one part of the animal's own blood and two parts of activated sterile trypsin,† incubated for 24 to 36 hours prior to operation at 37 C, was introduced into the pancreas under an injection pressure of 140 to 150 mm. Hg. The accessory pancreatic duct was ligated as the polyethylene catheter was removed. Duodenotomy openings were closed with a double layer of continuous absorbable surgical (gut) sutures.

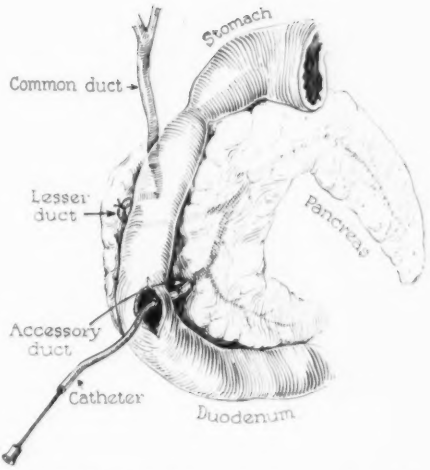


Fig. 1.—Method of injecting the pancreatic duct system.

Animals were divided into four groups: 1. Twenty controls, which received no treatment but were allowed food and water as desired. 2. Steroid-treated animals (15), which received 100 mg. of hydrocortisone intravenously during the operative procedure and 100 mg. of cortisone acetate intramuscularly immediately after operation. Thereafter, these animals received 50 mg. of cortisone acetate intramuscularly twice daily for five days, 50 mg. once daily for two days, and 25 mg. once daily for two days. 3. Antibiotic-treated animals (15), which received 400,000 units of penicillin and

* Veterinary Nembutal sodium contains per cubic centimeter 60 mg. of pentobarbital sodium, 10% alcohol, and 20% propylene glycol in water.

† The trypsin solution was prepared by mixing crystalline lyophilized trypsin (Tryptar) with 25 cc. of a sterile phosphate buffer solution. This resulted in a trypsin solution with 10,000 units per cubic milliliter.

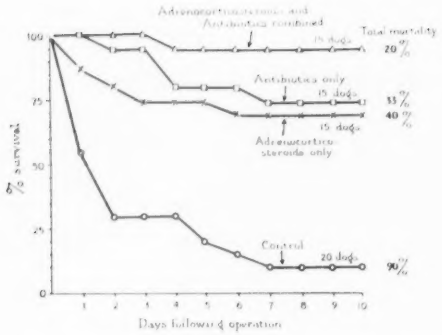


Fig. 2.—Acute hemorrhagic pancreatitis. Comparison of results in treated animals and in control series.

0.5 gm. of streptomycin at the completion of the operative procedure and daily thereafter for one week. 4. Animals (15), receiving a combination of antibiotic and steroid therapy, as described above.

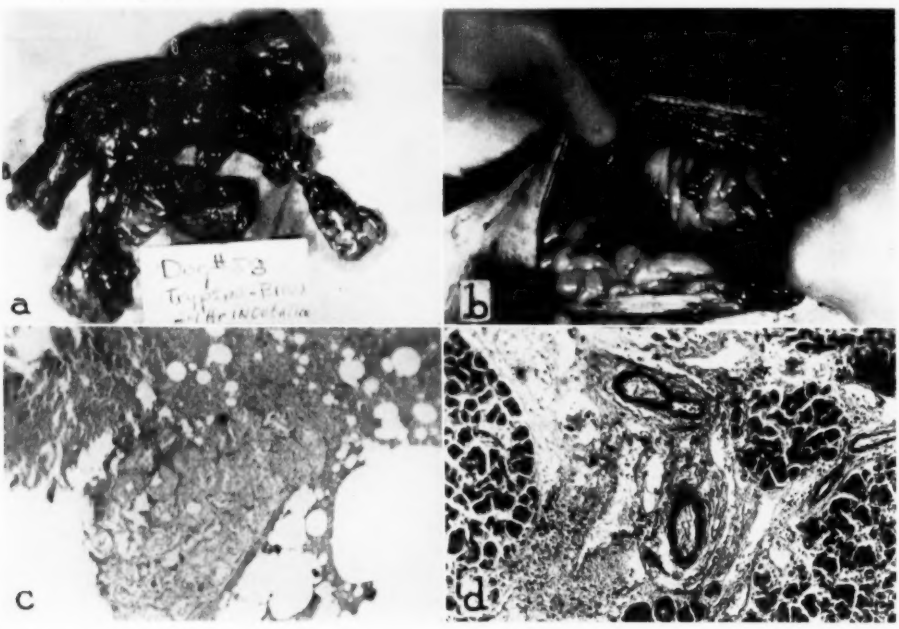
Necropsy was performed as soon as possible on all animals that died in the postoperative period. Survivors were allowed to recover for at least three weeks prior to being killed.

Results

A comparison of the responses of untreated and of treated animals is shown in Figure 2, with the per cent of survivors plotted against the survival time in days for the first 10 days following operation.

1. *Controls.*—Of 20 untreated animals, 18 (90%) died during the first 10 days following operation. In 14 the course was fulminant, characterized by extreme lethargy, prostration, signs of shock, and death within the first 48 hours following surgery. Autopsy revealed a severe acute hemorrhagic pancreatitis with marked fat necrosis and serosanguineous abdominal fluid (Fig. 3). The two survivors were killed at 23 and 43 days, respectively. These animals had appeared ill immediately after operation but recovered, and at autopsy the pancreas was found to be reduced in size, pale, indurated, and covered with dense adhesions.

Fig. 3.—Gross and microscopic findings in an animal which died 24 hours after operation with no treatment. (*a*) Severe hemorrhage and glandular necrosis; (*b*) serosanguineous fluid present in abdomen; (*c*) fat necrosis; (*d*) typical microscopic findings, including acinar necrosis, edema, arteritis of small vessels, and polymorphonuclear-cell infiltration. Reduced to 87% of mag. × 100.



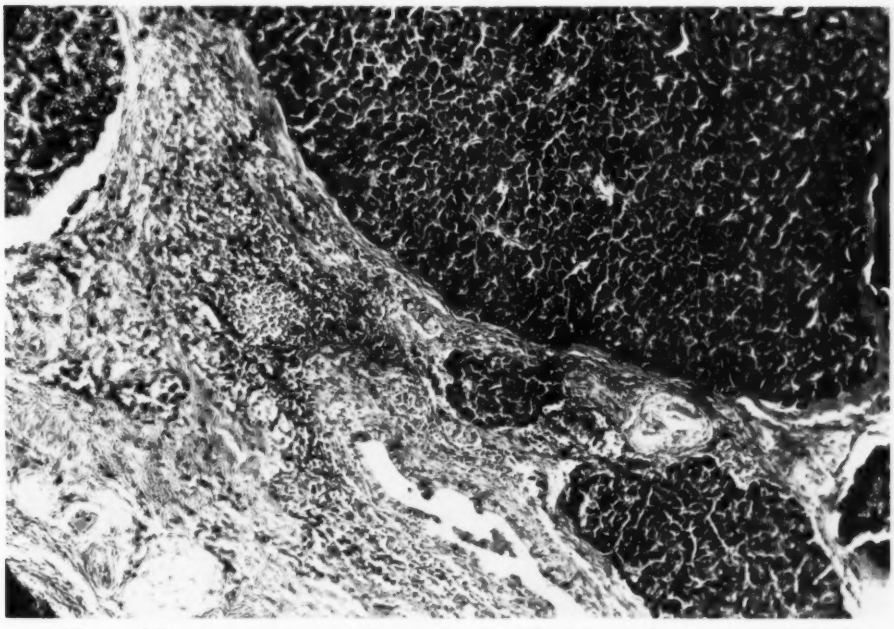


Fig. 4.—Microscopic appearance of pancreas removed after complete recovery of animal treated with adrenocorticosteroids. Good preseveration of lobules. Interstitial spaces filled with connective tissue. One small inflammatory focus. Reduced to 90% of mag. × 100.

2. *Steroids Alone.*—Of 15 animals, 6 (40%) receiving adrenocorticosteroids as the only treatment died, and 5 deaths occurred during the first 10 days. The other animal died on the 21st day, and no autopsy was performed. Three animals died during the first 48 hours, each with autopsy findings of severe pancreatitis. The nine survivors were followed for one month or longer and appeared to make a complete recovery. At autopsy the pancreas from these animals was found to be atrophic, due to duct ligation, indurated, and surrounded with adhesions. Occasionally small foci of infection were observed microscopically (Fig. 4).

During the immediate postoperative period, the clinical course in this group differed from that of the control animals. Almost without exception the dogs were able to stand in the cage, appeared alert, and were able to eat.

3. *Antibiotics Alone.*—Of 15 animals, 5 (33%) receiving antibiotics as the only therapy died, and 4 deaths occurred during the first 10 days. Only one dog died during the first 48 hours. The fifth animal died on the 23d day. Severe pancreatic necrosis and serosanguineous abdominal fluid were present in all five animals. Survivors were followed for at least one month, and recovery appeared to be complete, although the immediate postoperative course was characterized by longer periods of lassitude, anorexia, and weakness than was observed in the animals receiving only adrenocorticosteroids. Pathologic findings at autopsy were similar to those observed in the steroid-treated group.

4. *Steroids and Antibiotics Combined.*—Only 3 of 15 animals treated with both antibiotics and adrenocorticosteroids died (20%). None of these animals died during the first 48 hours, and only one failed to survive the first 10 days following operation. Through an error, this animal received the antibiotic for only two, instead of seven, days. The other two deaths occurred 15 and 16 days, respectively, following operation, and both appeared to result

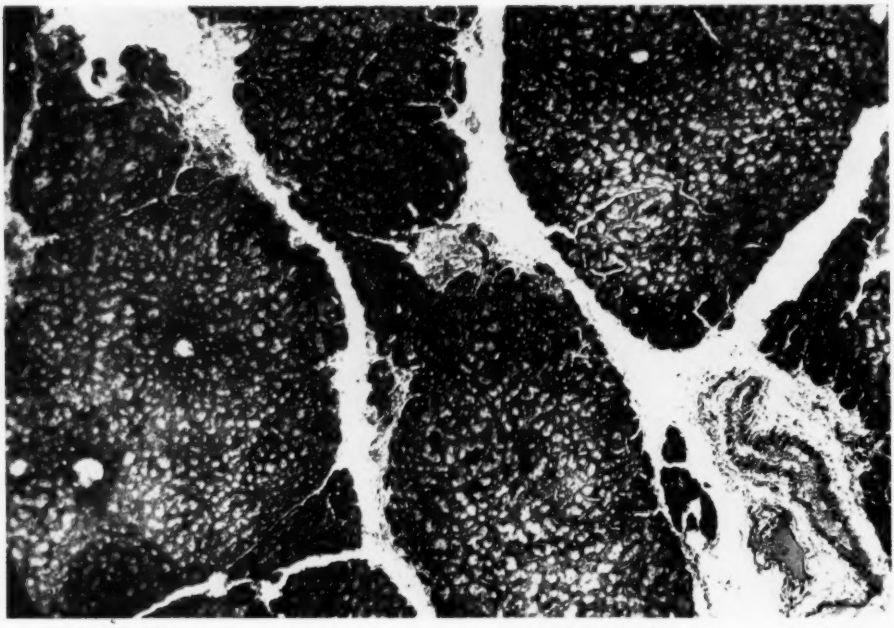


Fig. 5.—Microscopic appearance of pancreas removed after complete recovery of animal treated with steroids and antibiotics. Good preservation of acini and lobules, with slight interstitial fibrosis. Ductal dilatation due to complete ligation at time of operation. Reduced to 90% of mag. × 50.

from causes other than acute hemorrhagic pancreatitis (distemper and adhesive bowel obstruction). The immediate, as well as the late, postoperative course of survivors was remarkably uneventful. Animals were alert and active from the day following surgery and began to eat promptly after operation. Autopsy, at least one month following the production of pancreatitis, revealed only a reduction in the size of the gland and adhesions at the operative site. There was little evidence of active inflammatory reaction (Fig. 5).

Application of the χ^2-test resulted in a probability of less than 0.002 in each of these groups.

Comment

In several different forms of experimental pancreatitis, including the injection of bile, trypsin, bile salts, and combinations of trypsin and bile salts into the pancreatic ducts, we observed a wide variation in the severity of the resulting lesion.[2] There often appeared to be little correlation between the pathologic findings in these experimental preparations and those observed in the human form of the disease. The present studies were carried out on a form of canine pancreatitis previously described by Nemir and Drabkin,[14] which we believe compares favorably, both in clinical course and in pathologic findings, with that observed in man (Fig. 6). The exact etiologic factor or factors involved in human pancreatitis have so far eluded complete definition. Therefore, a beneficial response following treatment of experimentally produced pancreatitis is no guarantee that the same agent will prove effective in the human form of the disease.

The clinical reports of other investigators, and the two cases presented herein, suggest that adrenocorticosteroids may be of some benefit in acute hemorrhagic pancreatitis. However, because of the profound effect of this disease on fluid and electrolyte balance, a variety of therapeutic meas-

ures are instituted. This makes the evaluation of any one agent exceedingly difficult. In several of the cases reported, as well as in our Case 1, the patient's condition deteriorated despite the usual supportive measures, prompting the use of adrenocorticosteroids. Whether extensive treatment of shock and fluid and electrolyte imbalance would have been adequate for recovery in most instances is impossible to ascertain. The patients described above developed acute pancreatitis following operative procedures, and this form of the disease is frequently associated with an extremely high mortality.

Development of infection and abscess formation occurring in cases of pancreatitis treated with adrenocorticosteroids has been reported.[6,12,16] Our first patient developed an abdominal-wall and intra-abdominal infection, which drained spontaneously approximately 10 days following institution of adrenocorticosteroid therapy. However, it is possible that reentry of the abdomen on the second postoperative day may have contributed in part to this postoperative infection.

In the animals studied, adrenocorticosteroids and antibiotics administered separately and in combination had a beneficial

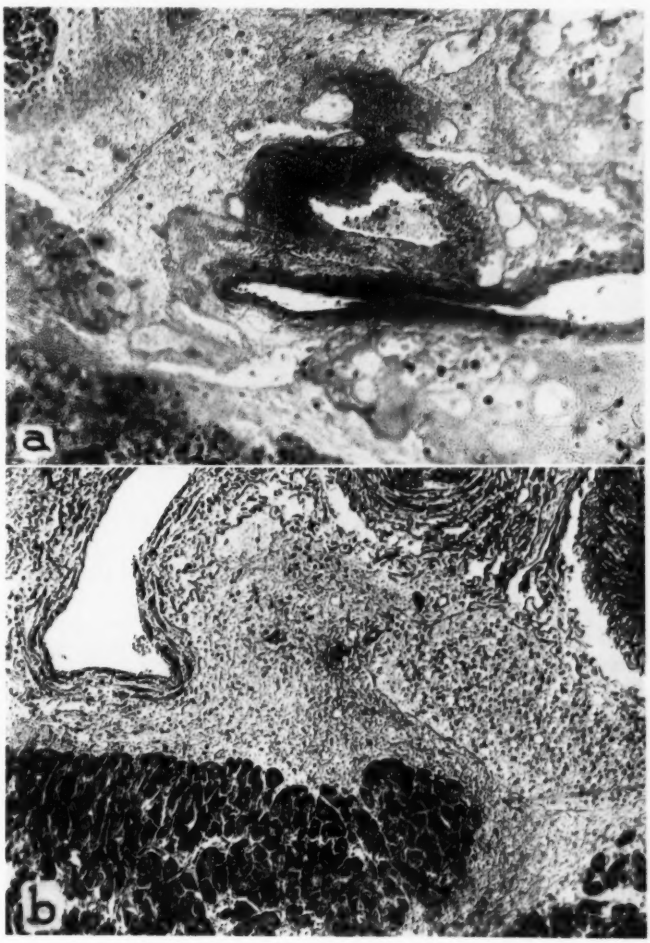


Fig. 6.—Comparison of microscopic picture in (*a*) human and (*b*) experimental canine pancreatitis. In both there are marked arteriolitis and phlebitis, interstitial edema, round-cell infiltration, and variable degrees of parenchymal necrosis. Vascular injury is marked in both cases. × 100.

effect on the clinical course of experimental pancreatitis when animals so treated were compared with untreated controls. Little difference was found when groups treated solely with adrenocorticosteroids and with antibiotics were compared. When these agents were combined, there was a remarkable difference between treated and untreated animals. In only one instance could the cause of death be attributed directly to pancreatitis, and this animal did not receive the entire course of antibiotic therapy.

One can but speculate upon the precise mechanism by which adrenocorticosteroids favorably influence the outcome of acute hemorrhagic pancreatitis. In the experimental animal, pathologic alterations in the pancreas include extensive inflammatory reaction in the walls of small arteries and veins, venous thrombosis, edema, inflammatory cellular infiltration, loss of blood into the interstitial tissues, and necrosis of the pancreatic parenchyma. Comparable changes are characteristic of the human form of disease (Fig. 6). A similar vascular response is typical of various forms of hypersensitivity reactions (anaphylaxis). If the basic lesion in acute pancreatitis is the result of acute vascular injury and ischemia with consequent pancreatic necrosis, as has been suggested,[1,3,15,18] then it is worth considering the plausibility of a vascular injury on the basis of local anaphylaxis originating from the action of some by-product formed when blood and trypsin are combined within the pancreas in the early stages of an acute hemorrhagic pancreatitis. If such an allergic mechanism were to contribute to the vascular injury present in human pancreatitis, then the modus operandi of adrenocorticosteroids would be more clearly defined. We are presently undertaking studies to clarify this point.

Summary

Two cases are presented in which an acute hemorrhagic pancreatitis occurring postoperatively was treated with adrenocorticosteroids, in conjunction with a wide variety of other supportive measures, to effect ultimate complete recovery. It is impossible to determine the relative importance of steroids, although in one instance the patient's condition continued to deteriorate despite other therapeutic adjuncts, including antibiotics, vasopressor drugs, fluids, and electrolytes.

In experimental animals, with a form of acute pancreatitis quite similar to that noted in humans, adrenocorticosteroids, when given alone, effected a definite reduction in mortality and improvement in clinical course. A similar response followed the use of penicillin and streptomycin. The results obtained when antibiotics and adrenocorticosteroids were combined were more favorable than those observed when the two agents were utilized separately.

The explanation for this improvement is as yet not clear. The severe vascular injury observed in both human pancreatitis and the experimental lesions produced in this study suggests that a local tissue hypersensitivity reaction may be an important etiologic factor.

These experimental findings, when considered in light of the limited clinical experience available, suggest that adrenocorticosteroids are worthy of further trial as an adjunct in the treatment of human pancreatitis.

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REFERENCES

1. Adams, T. W., and Musselman, M. M.: Pancreatic Venous Thrombosis as an Etiologic Factor in Acute Necrotizing Hemorrhagic Pancreatitis, S. Forum 4:401, 1953.

2. Anderson, M. C.; Van Hagen, F.; Method, H. L., and Mehn, W. H.: An Evaluation of the Use of Bile, Bile Salts, and Trypsin in the Production of Experimental Pancreatitis, Surg. Gynec. & Obst. 107:693, 1958.

3. Block, M. A.; Wakim, K. G., and Baggenstoss, A. H.: Experimental Studies Concerning Factors in the Pathogenesis of Acute Pancreatitis, Surg. Gynec. & Obst. 99:83, 1954.

4. Bloodworth, A. F., and Cohen, S. L.: Cortisone in Treatment of Acute Pancreatitis Associated with Mumps: Epidemic Parotitis, U. S. Armed Forces M. J. 7:285, 1956.

5. Bockus, H. L.; Kalser, M. H.; Roth, J. L. A.; Bogoch, A. L., and Stein, G.: Clinical Features of Acute Inflammation of the Pancreas, A. M. A. Arch. Int. Med. 96:308, 1955.

6. Brockis, J. G., and Jones, E. T.: Treatment of Acute Hæmorrhagic Pancreatitis with Cortisone, Brit. M. J. 2:1524, 1956.

7. Comfort, M. W.: Treatment of Pancreatitis, A. M. A. Arch. Int. Med. 95:735, 1955.

8. Elman, R.: Discussion of Symposium on Pancreatitis, Gastroenterology, 28:588, 1955.

9. Eskwith, I. S.; Cacace, V. A., and Sollosy, A.: Acute Hemorrhagic Pancreatitis: Treatment with Cortisone, New England J. Med. 252:494, 1955.

10. Hoste, O.: Effects of Cortisone (Adrenocortical Preparation) Therapy in Pancreatitis During Infectious Hepatitis: Case, Belg. tijdschr. geneesk. 9:492, 1953.

11. Jones, C. A.: Medical Management of Acute Pancreatitis, A. M. A. Arch. Int. Med. 96:332, 1955.

12. Kaplan, M. H.: Acute and Chronic Relapsing Pancreatitis: The Clinical Implications of Their Acceptance as Diseases of Adaptation, Am. J. Gastroenterol. 25:234, 1956.

13. Mouchet, A., and Albahary, C.: Pancréatite aiguë hémorragique et hormones corticotropes, Presse méd. 63:706, 1955.

14. Nemir, P., Jr., and Drabkin, D. L.: The Pathogenesis of Acute Necrotizing Hemorrhagic Pancreatitis: An Experimental Study, Surgery 40:171, 1956.

15. Popper, H. L.; Necheles, H., and Russell, K. C.: Transition of Pancreatic Edema into Pancreatic Necrosis, Surg. Gynec. & Obst. 87:79, 1948.

16. Rogers, N. C.; Wilson, A. O.; Meynell, M. J., and Cooke, W. T.: Treatment of Acute Pancreatitis with Cortisone, Lancet 2:651, 1956.

17. Solem, J. H.; Knutrud, O., and Andresen, K. R.: Treatment of Acute Pancreatitis with Cortico-Depot, Acta chir. scandinav. 109:415, 1955.

18. Smyth, C. J.: Etiology of Acute Hemorrhagic Pancreatitis with Special Reference to Vascular Factors: An Analysis of Autopsies and an Experimental Investigation, Arch. Path. 30:651, 1940.

19. Stephenson, H. E., Jr.; Pfeffer, R. B., and Saypol, G. M.: Acute Hemorrhagic Pancreatitis: Report of a Case with Cortisone Treatment, A. M. A. Arch. Surg. 65:307, 1952.

DISCUSSION

DR. HAROLD L. METHOD, Chicago: When we embarked on this problem, we experienced considerable frustration. It soon became apparent that it was very difficult to produce a standard uniform lesion of acute hemorrhagic pancreatitis in the dog. Early we found that in our dogs studied there was at least a 60% functional communication between the lesser and the greater pancreatic duct. This, of course, allowed a reflux of the injected material into the duodenum, and, naturally, there was considerable variation in the results of the severity of the lesion. This has been observed by others, and we have now routinely ligated the lesser pancreatic duct.

In our hands the injection of bile, bile salts, trypsin, or combinations of these, failed to produce a uniform acute hemorrhagic pancreatitis. We finally adopted a modification of the method suggested by Niemeier and Drabkin, in which they used the dog's own blood and pancreatic juice. We used activated trypsin, which was incubated for 24 to 36 hours at 37 C. We also controlled the volume of injection and the pressure. Using this method, we felt we were able to get a consistent acute hemorrhagic pancreatitis which was quite similar to the human form of the disease.

[Slide] This is the microscopic section of one of our control dogs with acute hemorrhagic pancreatitis. You will note the endarteritis, the thrombosis in the veins, extensive inflammatory reaction, the edema in the interstitial tissue, and the pancreatic necrosis.

[Slide] This is a case of human acute hemorrhagic pancreatitis. Again you see the arteritis, phlebitis and thrombosis, extensive inflammatory edema in the interstitial tissues, and the pancreatic panenchymal necrosis, which is quite similar to what we have produced in the dog.

One can only speculate as to the mechanism by which adrenocorticosteroids favorably influence the course of this disease. Similar vascular changes are also characteristic of various types of hypersensitivity reactions. If the basic lesion in acute hemorrhagic pancreatitis is acute vascular injury with ischemia and subsequent parenchymal necrosis, as many investigators have suggested, it is worth considering the plausibility of a vascular injury on the basis of anaphylaxis originating from the action of some by-product formed when blood and trypsin are combined within the pancreas in the early stages of an acute hemorrhagic pancreatitis. If such an allergic mechanism were to contribute to the vascular injury present in human pancreatitis, the modus operandi of adrenocorticosteroids would be more clearly defined. The study also suggests that if adrenocorticosteroids are used they should be used early to prevent this anaphylactoid-type reaction.

Excretion of Antibiotics in Pancreatic Fluid

FREDERICK W. PRESTON, M.D.; MILTON SILVERMAN, Ph.D., and GEORGE C. HENEGAR, M.D., Chicago

Drainage of pancreatic juice uncontaminated by bile or intestinal contents is observed infrequently in clinical practice. Two such patients seen recently gave us the opportunity of determining the excretion of antibiotics by the pancreas. The excretion of erythromycin, streptomycin, and chloramphenicol in fluid collected by means of a T-tube in the main pancreatic duct was measured in a patient with chronic relapsing pancreatitis and the results reported.[2] Subsequently, tetracycline was found not to be excreted in pancreatic fluid of this patient after intravenous administration. This report concerns assays made in the second patient, to whom, in addition to the four antibiotics mentioned above, oleandomycin and Sigmamycin (a combination of tetracycline and oleandomycin buffered with ascorbic acid) were given.

Report of a Case

A 45-year-old white man was admitted to the Veterans Administration Research Hospital on July 22, 1957, with an eight-day history of pain in the epigastrium, nausea, and vomiting. The pain had remained severe for 36 hours after onset and had gradually subsided. The nausea and vomiting had persisted, and he had been unable to retain anything taken by mouth. His alcoholic intake had been about 2 qt. of beer a day for several years. On physical examination he appeared dehydrated. There was a palpable mass in the epigastrium, and a large mass, pushing the stomach forward, was visualized roentgenographically after barium meal. On July 27 he suddenly developed severe pain in the epigastrium, and soon afterward was found to have a rigid, tender, and distended abdomen. Leukocyte count at this time was 20,000 per cubic millimeter. Laparotomy revealed a large cyst of the pancreas with a small area of perforation. There was a straw-colored fluid in the peritoneal cavity. On opening the mass a large cystic cavity was found. This was treated by suturing the walls of the cyst to the abdominal wall, thus creating a fistula which drained clear pancreatic fluid, averaging approximately 275 cc. daily. No bilirubin was present in the fluid when tested on several occasions. Roentgenograms made after the injection of iodized oil U. S. P. (Lipiodol) on Oct. 8 showed a small sinus tract with no communication with the biliary or intestinal tract. On Nov. 26 a laparotomy was done and the fistula was implanted into a loop of jejunum.

Methods

The pancreatic fluid was obtained by means of a catheter placed into the fistula. It was found that leakage around the catheter and subsequent excoriation of the skin could be prevented by slight continuous suction, using a sump-type catheter. Collections from the catheter were passed through a Seitz filter for sterilization. Blood samples obtained by venipuncture were allowed to clot and the serum drawn off, using sterile precautions. Assays were done of antibiotics in blood and pancreatic fluid before and after administration of antibiotics, using a modification of the tube dilution method.[3] The method of Price, Nielsen, and Welch was used for streptomycin.[6] The pH of freshly collected pancreatic fluid was 7.9 to 8.1. The nutrient broth used as the culture medium was buffered with phosphate buffer to give a pH of 8.0 when erythromycin, streptomycin, and oleandomycin were assayed, a pH of 7.0 for Sigmamycin, a pH of 6.0 for chloramphenicol, and a pH of 4.5 for tetracycline. Organisms isolated by routine sensitivity tests in the clinical laboratory and sensitive to 0.5μg. per milliliter or less of antibiotics were selected for test organisms in order to detect small quantities of antibiotics in pancreatic juice. These organisms were more sensitive to antibiotics than those recommended for these assays.[3]

Results

Erythromycin.—Figure 1 shows the concentration of erythromycin in the blood and

Aided by a grant from Chas. Pfizer & Company.

Eli Lilly & Company and Chas. Pfizer & Company supplied the antibiotics used in these studies.

Read at the 66th Annual Meeting of the Western Surgical Association, Rochester, Minn., Nov. 21, 1958.

From the Departments of Surgery and Bacteriology, Veterans Administration Research Hospital and Northwestern University Medical School.

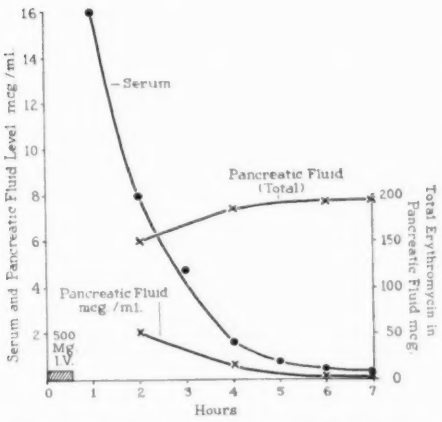

Fig. 1.—Excretion of erythromycin in pancreatic fluid following an intravenous dose of 500 mg. in 250 ml. of isotonic saline given over a 30-minute period.

pancreatic fluid and the total amount excreted for a seven-hour period following the intravenous injection of 500 mg. of erythromycin glucoheptonate. The highest concentration in serum was 16μg/ml. and was observed one hour after the injection was begun. The highest concentration in pancreatic fluid occurred two hours after the injection was begun and was 2μg/ml., which is 12.5% of the highest concentration in the serum. The total amount of erythromycin which appeared in pancreatic fluid during the seven-hour period was 192μg., which was approximately 0.04% of the total dose given.

Streptomycin.—Concentrations of streptomycin in serum and pancreatic fluid after an intramuscular injection of 500 mg. of streptomycin sulfate are shown in Figure 2. The highest concentration in the serum was 16μg/ml. and was observed one and two hours after the injection. The highest concentration in pancreatic fluid was 2μg/ml. and was observed two and four hours after the injection. The total amount excreted (241μg.) amounted to 0.05% of the total dose given.

Chloramphenicol.—Chloramphenicol was detected in pancreatic fluid, as indicated in Figures 3 and 4 after oral and intravenous administration when the assays were conducted at pH 6.0. After the oral dose, the highest level in the serum was 16μg/ml., and the highest level in pancreatic fluid was 2μg/ml. After intravenous administration, the highest serum level was 20μg/ml., and the highest level in pancreatic fluid was

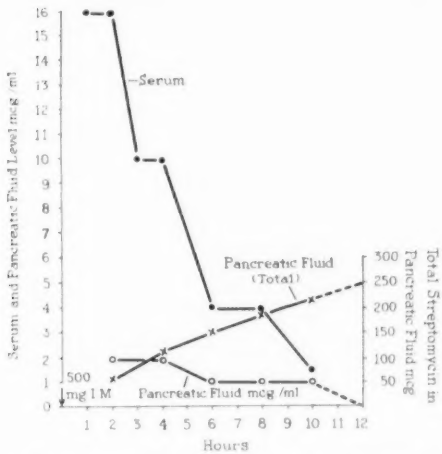

Fig. 2.—Excretion of streptomycin in pancreatic fluid after an intramuscular dose of 500 mg. The determination at 12 hours indicated that there was less than 1μg/ml. of streptomycin in pancreatic fluid. Therefore the concentrations are projected as dotted lines.

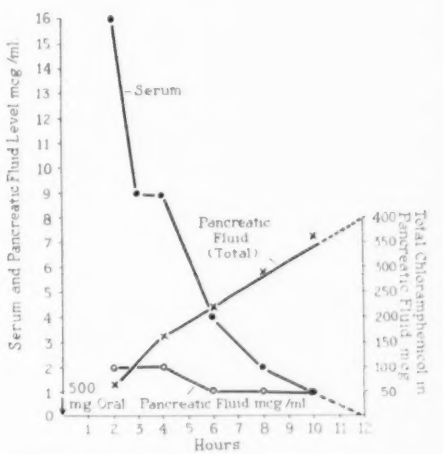

Fig. 3.—Excretion of chloramphenicol in pancreatic fluid after an oral dose of 500 mg. The determination at 12 hours indicated that there was less than 1μg/ml. of chloramphenicol in pancreatic fluid. Therefore the concentrations are projected as dotted lines.

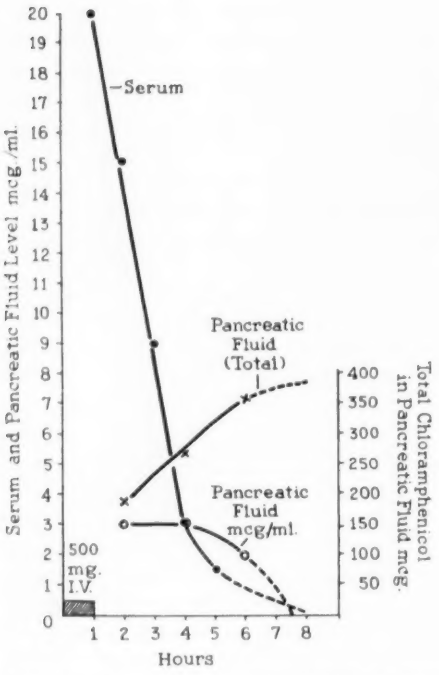

Fig. 4.—Excretion of chloramphenicol in pancreatic fluid after an intravenous dose of 500 mg. in 250 ml. of isotonic saline given over a one-hour period. The determinations at eight hours indicated that there was less than 1μg/ml. of chloramphenicol in serum and pancreatic fluid. Therefore the concentrations are projected as dotted lines.

3μg/ml. The amount of the drug appearing in pancreatic fluid was 0.07% and 0.08% of the total dose, depending upon whether it was given intravenously or orally. No chloramphenicol could be detected when the assay was run in unbuffered media, the pH of which varied between 7.5 and 8.0.

Oleandomycin.—Figure 5 shows that the highest level of oleandomycin in serum was 6μg/ml. and occurred one hour after beginning an intravenous dose of 500 mg., given over a 60-minute period. The highest level in pancreatic fluid also occurred at the one-hour period and was 2.4μg/ml. (40% of the highest level in serum). The total amount of oleandomycin appearing in pancreatic fluid was 375μg., which was 0.08% of the dose administered.

Tetracycline and Sigmamycin.—These drugs were given intravenously in 500 mg.

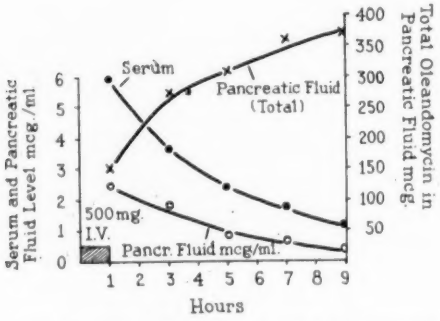

Fig. 5.—Excretion of oleandomycin in pancreatic fluid after an intravenous dose of 500 mg. in 250 ml. of isotonic saline given over a one-hour period.

doses. Serum levels of 12μg/ml. were obtained with each. Neither was detected in pancreatic fluid during the following 12 hours, assays being made at two-hour intervals.

Sigmamycin is a mixture of one-third oleandomycin and two-thirds tetracycline. Because of the synergistic action of these antibiotics in this combination, it is possible to isolate organisms sensitive to Sigmamycin and resistant to oleandomycin and tetracycline. Such an organism was used to detect Sigmamycin in serum and pancreatic fluid. Other organisms were then isolated and used separately for tetracycline and oleandomycin. This single specificity of micro-organisms is the explanation for the presence of oleandomycin and the absence of Sigmamycin and tetracycline in pancreatic fluid.

Comment

A summary of these experiments in given in Table 1, and for comparison the results

TABLE 1.—*Maximum Concentration of Antibiotics*

Drug	Dose	Serum, μg/Ml.	Pancreatic Fluid, μg/Ml.
Erythromycin	0.5 gm. I. V.	16	0.5
Chloramphenicol	0.5 gm. I. V.	20	3.0
Chloramphenicol	0.5 gm. oral	16	2.0
Streptomycin	0.5 gm. I. M.	16	2.0
Oleandomycin	0.5 gm. I. V.	6	2.4
Sigmamycin	0.5 gm. I. V.	12	none
Tetracyline	0.5 gm. I. V.	12	none

TABLE 2.—*Maximum Concentration of Antibiotics*

Drug	Dose	Serum, μg/Ml.	Pancreatic Fluid, μg/Ml.
Erythromycin	0.5 gm. I. V.	16	1.6
Chloramphenicol	0.5 gm. oral	10	1.0
Streptomycin	0.5 gm. I. M.	16	0.4
Tetracycline	0.5 gm. I. V.	..	None

which were obtained with the patient previously reported,[2] which are essentially similar, are given in Table 2. Work done by others has shown that oxytetracycline (Terramycin) and chlortetracycline (Aureomycin) do not appear in pancreatic juice after systemic administration.[6,10,11] Our work indicates that the same is true for tetracycline and confirms previous reports that streptomycin is secreted in small concentrations.[6,10] The highest concentrations of streptomycin in pancreatic fluid were 2.0μg/ml. in the patient with the marsupialized cyst and 0.4μg/ml. in the patient with pancreatitis. According to Youmans and Fisher,[12] some strains of the enterococcus group and of Escherichia coli are inhibited by concentrations of streptomycin in this range. Murray and Finland[8] have shown that streptomycin is three times as active against Gram-negative bacilli at pH 8.0 as at lower pH levels. For these reasons, streptomycin would appear to be a useful drug for systemic therapy in patients with infected fistulas.

Miller and Wiper[7] showed that sulfanilamide appears in pancreatic fluid, and Howard and associates[6] showed that sulfadiazine is similarly secreted. These drugs appear in pancreatic fluid approximately in the same concentrations as in the blood. Howard and associates[5,6] demonstrated therapeutic concentrations of penicillin in pancreatic fluid in man, but this was not confirmed by Rumore, Olander, and Puestow.[10] Penicillin in pancreatic juice may be inactivated by penicillinase-producing bacteria,[6] which may have been present in the fistula studied by Rumore and associates.

Our results with chloramphenicol are at variance with previous reports,[6,10] in which none of the drug administered was recovered in pancreatic fluid. We readily detected chloramphenicol when the assay was done at pH 6.0 after oral or intravenous administration. Less chloramphenicol could be detected when the assays were run at pH 7.5 and none at pH 8.0. Organisms of a high degree of sensitivity were used for these assays, which might have been negative had organisms less sensitive to the drug been employed.

The secretion of erythromycin and oleandomycin in pancreatic fluid have not been reported previously. According to Herrell, the concentration of erythromycin necessary to inhibit the growth of sensitive organisms is 0.2μg/ml. to 2.0μg/ml.[4] In our experiment, the level of erythromycin in serum remained within this therapeutic range for the seven hours during which it was studied. The level in pancreatic fluid was within this range when determined two and four hours after beginning intravenous injection. Erythromycin, like streptomycin, is more active at pH 8 than at pH 7.

The highest level of oleandomycin in pancreatic fluid was 2.4μg/ml., which is 40% of the highest level in serum. This concentration is sufficiently high to be therapeutically effective.

Erythromycin and oleandomycin would appear to be therapeutically effective in the treatment of fistulas infected with sensitive organisms, because both are excreted in adequate concentrations and both are active at the pH of pancreatic fluid.

Summary

Erythromycin and oleandomycin appeared in pancreatic fluid after intravenous administration in concentrations sufficient to inhibit organisms sensitive to these antibiotics.

Streptomycin is excreted in pancreatic fluid in small concentrations. The concentrations were high enough to provide antibacterial effect against some organisms.

Chloramphenicol was detected in pancreatic fluid when assayed at pH 6.0. It was not detected at pH 8.0.

Sigmamycin and tetracycline were not detected in pancreatic fluid after intravenous administration.

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REFERENCES

1. Flippin, H. F., and Eisenberg, G. H.: Antimicrobial Therapy in Medical Practice, Philadelphia, F. A. Davis Company, 1955.

2. Gerber, B.; Silverman, M., and Preston, F. W.: The Excretion of Antibiotics in Pancreatic Fluid, S. Forum 7:261, 1957.

3. Grove, D. C., and Randall, W. A.: Assay Methods of Antibiotics, New York, Interscience Encyclopedia, Inc., 1955.

4. Herrell, W. E.: Erythromycin, New York, Interscience Encyclopedia, Inc., 1955.

5. Howard, J. M.; James, C. L., and Evans, S. S.: Physiological Studies on the External Pancreatic Secretions in Man, S. Forum 7:577, 1957.

6. Howard, J. M.; Pulaski, E. J., and Fusillo, M. H.: The Pancreatic Secretion of Antibiotics and Sulfadiazine in Man, S. Forum p. 236, 1952.

7. Miller, J. M., and Wiper, T. B.: Physiologic Observations on Patients with External Pancreatic Fistula, Ann. Surg. 120:852, 1944.

8. Murray, R., and Finland, M.: Effect of pH on Streptomycin Activity, Am. J. Clin. Path. 18:247, 1948.

9. Price, C. W.; Nielsen, J. K., and Welch, H.: Estimation of Streptomycin in Body Fluids, Science 103:56, 1946.

10. Rumore, P. C.; Olander, G. A., and Puestow, C. B.: Excretion of Antibiotics, Dyes, and Radioactive Substances Through External Pancreatic Fistula, Surgery 34:735, 1953.

11. Sinclair, I. S. R.: Observations on a Case of External Pancreatic Fistula in Man, Brit. J. Surg. 44:250, 1956.

12. Youmans, G. P., and Fisher, M. W.: Action of Streptomycin on Micro-Organisms in Vitro, in Streptomycin: Nature and Practical Applications, edited by S. A. Waksman, Baltimore, Williams & Wilkins Company, 1949, Chap. 7.

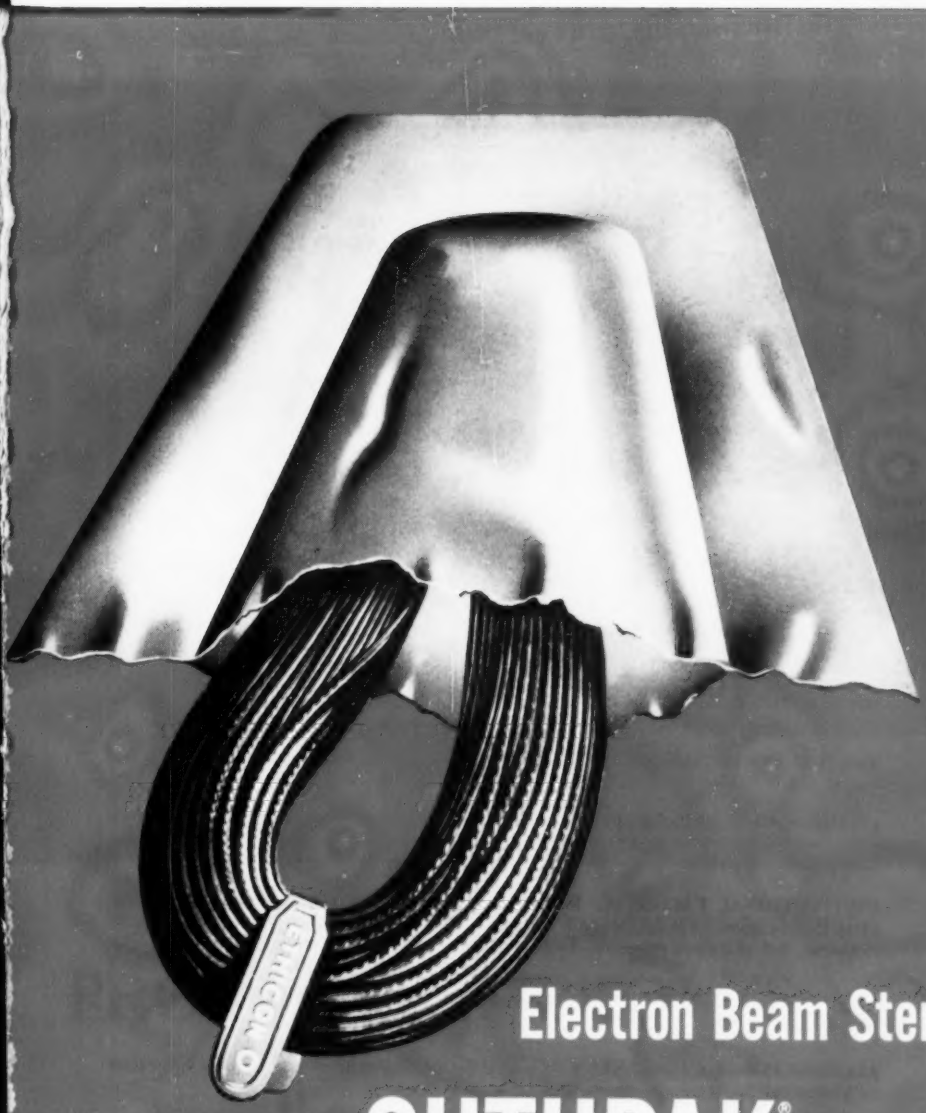
DISCUSSION

DR. CHARLES PUESTOW, Chicago: When Dr. Preston asked me to discuss this paper, he said he did so because he was citing some work that we did. We carried out studies similar to his, and our results also showed that some antibiotics were secreted through a pancreatic fistula. Although our results do not entirely agree with his, I think it is probably because Dr. Preston did a more scientific piece of work than we did. However, it is of interest and of value, as he has pointed out, that if we know what organisms contaminate the pancreas in chronic and relapsing pancreatitis, and what antibiotics are most likely to be of value, we may be able to hold infection down until we can take care of the obstruction in a surgical manner. The infection is definitely a secondary consideration in chronic relapsing pancreatitis, and Dr. Gillesby and I both believe firmly that the great majority of cases have some degree of ductal obstruction. Until that is taken care of we are not going to correct the disease.

Some years ago, before this group, I brought out the importance of more and more research on the pancreas, and it is gratifying to see that a great deal more work is being done and that we are beginning to get some light on the handling of one of the most difficult abdominal surgical problems.

Another thing in our work that I think is of interest is that we attempted to follow out the common procedure spoken of as "drying up" the pancreas by using methantheline (Banthine) and constant gastric suction. We found that the amount of secretion from the fistula was cut down by approximately 70%, but that the amount of amylase and lipase is increased, and that the viscosity of the secretion was also greatly increased.

It poses a problem—that by drying up the pancreatic secretion, we may increase viscosity, leading to plugging of the ducts and aggravating the disease, and that the increased concentration of enzymes may lead to increased digestion of the pancreas and the surrounding tissues. These are important considerations, and these studies ought to be carried on further, to be either substantiated or refuted. It is gratifying to see this work being done on the pancreas, and I think the authors have done excellent work.



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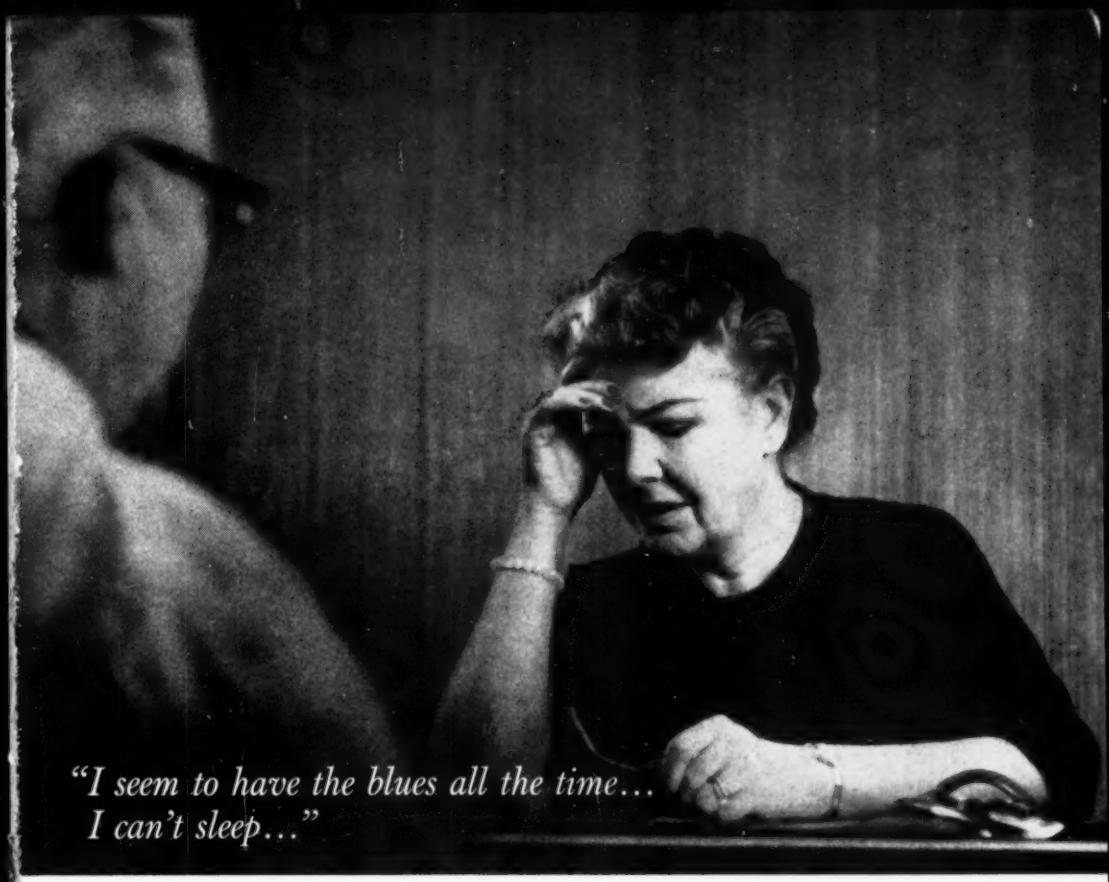

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References:
1. Alexander, L.: J.A.M.A. 166:1019, March 1, 1958.
2. Current personal communications; in the files of Wallace Laboratories.
3. Pennington, V.M.: Am. J. Psychiat. 115:250, Sept. 1958.

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1. *Rushia, E. L.: Preliminary report on the use of meprobamate for pre-anesthetic sedation. J.M.A. Georgia* **46**:*93, March 1957.*
2. *Lamphier, T. A.: The role of meprobamate in postoperative surgical care. Ann. New York Acad. Sc.* **67**:*810, May 9, 1957.*
3. *Kern, E. C.: Preoperative sedation with meprobamate (Miltown) in surgery of eye, ear, nose and throat. Eye, Ear, Nose & Throat Month.* **36**: *408, July 1957.*

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Essential Amino Acids Pattern in Quaker Oats Breakfast Dish* (1)	1.0	3.8	4.2	2.9	4.7	1.4	6.4	4.3
Essential Amino Acids Pattern Required by Male Adults (2)	1.0	4.4	3.2	2.0	3.2	4.4	4.4	2.8

*Prepared from 1 oz. Quaker Oatmeal (dry) and 4 fl. oz. whole milk.

(1) Estimated from values in "Amino Acid Content of Foods", Home Economics Research Report No. 4, U.S. Dept. Agr., 1957, pp. 48, 58. (Quaker Oats protein = 16.7%)

(2) Staff Report, "Rose Reports Human Amino Acid Requirements", Chem. Eng. News 27:1364 (1949).

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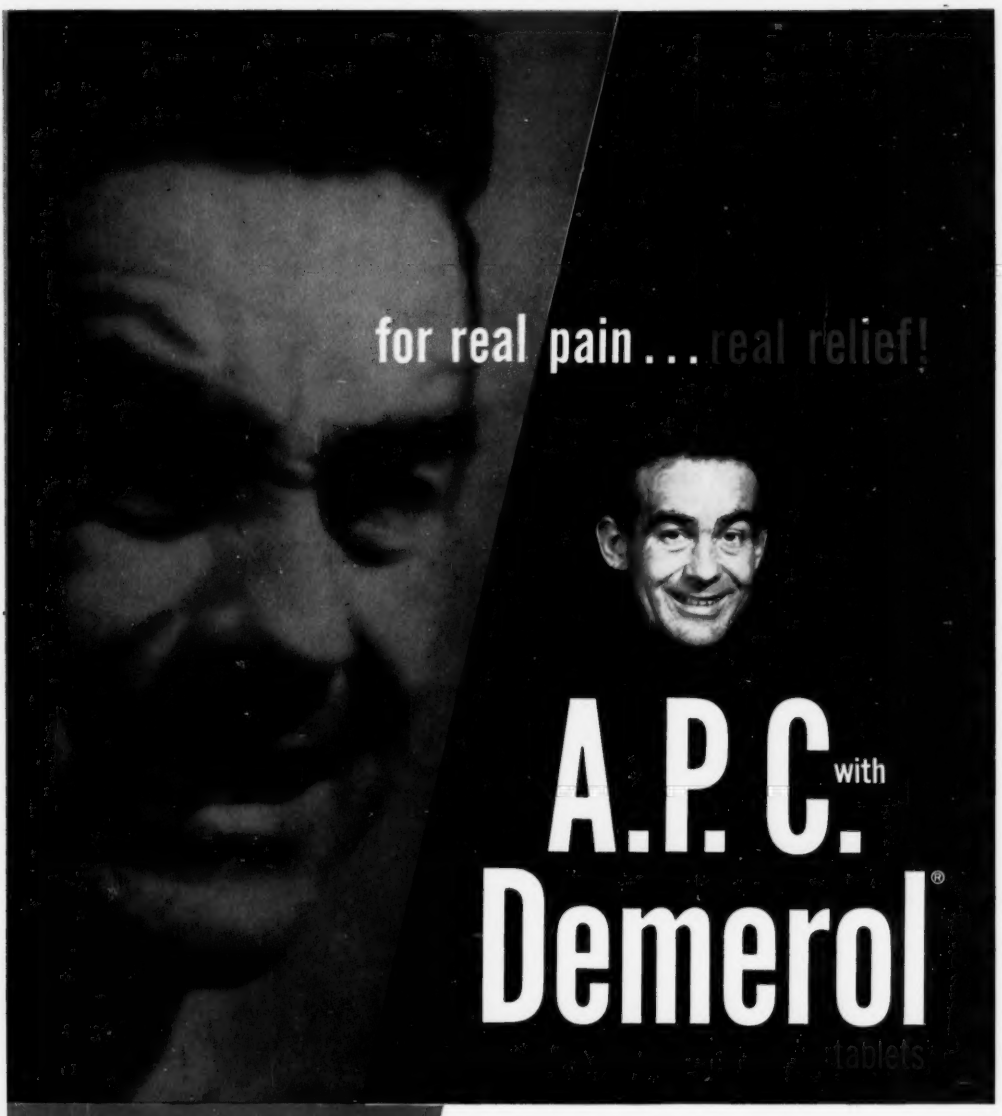

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